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Assessing the Impacts of Smoking and Obesity on Mortality and Morbidity in the United States

Abstract

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in the United States

Bochen Cao

Michel Guillot

Smoking and obesity are two leading risk factors that account for the current US lags in advances in health and longevity compared to other wealthy nations. This dissertation consists of three independent studies of the impacts of smoking and obesity on population health outcomes among older adults in the United States. The first study estimates the effects of the recent smoking decline on future all-cause mortality, based on the association observed between cohort smoking pattern and cohort death rates from lung cancer. We find that change in smoking is expected to have a large effect on U.S. mortality. However, compared to men, women are expected to have smaller increase in future life expectancy, because of their lagged decline in smoking. The second study extends the first one and estimates the joint effects of smoking and obesity on both mortality and disability. A multistate lifetable approach is applied to estimate the transition rates between different health states, which are in turn projected up to 2040 using a modified Lee-Carter model that incorporates cohort histories of smoking and obesity. The results indicate men and women both are expected to experience compression of disability, with increasing proportions of their future gain in life expectancy likely to be disability free. Nevertheless, due to gender difference in smoking history and in response to obesity, men will likely to have an advantage over women in health improvement in the next three decades. The third study investigates the direct effects of both obesity and weight change on mortality. A dynamic causal model is applied to adjust for reverse causality that is attributable to illness-associated and smoking-associated weight loss in a time-dependent fashion, a problem that prior studies often fail to adequately handle. This study demonstrates that both the confounding by illness and by smoking lead to overestimates of the effects of being underweight and of weight loss, but underestimates the effect of being obese. Moreover, not only being underweight or severe obese, but also sharp weight fluctuations are associated with excess mortality risk.

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ASSESSING THE IMPACTS OF SMOKING AND OBESITY ON MORTALITY AND MORBIDITY

IN THE UNITED STATES

Bochen Cao

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Demography

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Supervisor of Dissertation

Michel Guillot

Associate Professor of Sociology

Graduate Group Chairperson

Michel Guillot, Associate Professor of Sociology

Dissertation Committee

Michel Guillot, Associate Professor of Sociology

Samuel Preston, Professor of Sociology

Douglas Ewbank, Research Professor Emeritus of Sociology

ASSESSING THE IMPACTS OF SMOKING AND OBESITY ON MORTALITY AND MORBIDITY
IN THE UNITED STATES

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ABSTRACT

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Smoking and obesity are two leading risk factors that account for the current US lags in advances in health and longevity compared to other wealthy nations. This dissertation consists of three independent studies of the impacts of smoking and obesity on population health outcomes among older adults in the United States. The first study estimates the effects of the recent smoking decline on future all-cause mortality, based on the association observed between cohort smoking pattern and cohort death rates from lung cancer. We find that change in smoking is expected to have a large effect on U.S. mortality. However, compared to men, women are expected to have smaller increase in future life expectancy, because of their lagged decline in smoking. The second study extends the first one and estimates the joint effects of smoking and obesity on both mortality and disability. A multistate lifetable approach is applied to estimate the transition rates between different health states, which are in turn projected up to 2040 using a modified Lee-Carter model that incorporates cohort histories of smoking and obesity. The results indicate men and women both are expected to experience compression of disability, with increasing proportions of their future gain in life expectancy likely to be disability free. Nevertheless, due to gender difference in smoking

history and in response to obesity, men will likely to have an advantage over women in health improvement in the next three decades. The third study investigates the direct effects of both obesity and weight change on mortality. A dynamic causal model is applied to adjust for reverse causality that is attributable to illness-associated and smoking-associated weight loss in a time-dependent fashion, a problem that prior studies often fail to adequately handle. This study demonstrates that both the confounding by illness and by smoking lead to overestimates of the effects of being underweight and of weight loss, but underestimates the effect of being obese. Moreover, not only being underweight or severe obese, but also sharp weight fluctuations are associated with excess mortality risk.

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Chapter 1 Projecting the Effect of Changes in Smoking on Future Life Expectancy in the United States

Samuel H. Preston

Bochen Cao

Introduction

A wide variety of personal behaviors affect an individual's health. In the aggregate, these behaviors affect the health of populations. The leading behavior that has been singled out as especially damaging to the health of the US population is smoking. Estimates by the Centers for Disease Control suggest that 18% of deaths in the US in 2000 were attributable to smoking (Mokdad, Marks, Stroup, & Gerberding, 2004, 2005).

Uncertainty about the future impact of smoking is a central component of the uncertainty surrounding projections of future mortality (Technical Panel, 2011). According to simulations by the Office of the Actuary, the 75-year actuarial balance of the Old-Age and Survivors Insurance program of the Social Security Administration is more sensitive to variation in future mortality rates than it is to any other demographic or economic parameter except real wages (Trustees, 2012). A reliable projection of the effect of smoking on future life expectancy would contribute to a better understanding of the fiscal future of the United States (King & Soneji, 2011; Soneji & King, 2012).

In this paper, we estimate the effects of declining smoking on mortality at ages 40+ in the United States over the period 2010-2040. Our estimates incorporate information about cohorts' smoking history, allowing mortality rates to be a function not only of current smoking pattern but also of the past. Duration of smoking is strongly

related to mortality risks among current smokers (Thun et al., 1997). An analytic advantage of incorporating smoking history into projections of future mortality levels is that many features of this history have already been observed and are not themselves products of an uncertain future.

Overview of Analytic Strategy

Our goal is to estimate the effect of changes in the lifetime distributions of smoking on future death rates. We take advantage of the fact that there is a clear marker of the impact of smoking histories on mortality: death rates from lung cancer. Smoking is the overwhelming factor accounting for variation in lung cancer mortality. Among US men aged 30 and older in 2005, it is estimated that 90% of lung cancer deaths are attributable to smoking; for females, the figure is 84-85% (Oza, Thun, Henley, Lopez, & Ezzati, 2011). Consistent with a major role for behavioral histories, death rates from lung cancer are organized on a cohort basis in the United States and elsewhere. This feature permits the identification of “cohort effects” that can be projected into the future as cohorts age. The final step in our analysis is translating projected death rates from lung cancer into all-cause mortality rates, using statistical relations that have been developed between smoking’s impact on lung cancer and its impact on all-cause mortality.

Another goal is to estimate the proportionate effect of changes in smoking on age-specific death rates. Our comparison schedule is simply the age-specific death rates at baseline, 2009-2010, which reflect the behavioral histories that had been accumulated at that point. We are not attempting to project mortality rates themselves, only to estimate the effect of changes in smoking on mortality. If there are other sources of future change

in mortality, we are implicitly assuming that the effects of changes in these behaviors will be independent of them.¹

Projecting the Effects of Changes in Smoking

The risk of death from smoking is a function of a multitude of smoking-related behaviors, including the number of cigarettes smoked per day, the degree of inhalation, the filtration and tar content of the cigarette, and how each of these (and other) components of a smoking profile have developed over a lifetime. Historical information is important because of a long lag between smoking behavior and its effects on mortality. A single cross-sectional indicator of smoking prevalence cannot effectively capture these many dimensions. Prevalence-based estimates of smoking risks are also affected by imprecise classification of smoking status among participants. For example, the largest prospective study of smoking risks, the Cancer Prevention Study II (CPS II) included among “lifetime non-smokers” persons who had smoked but who had not reported themselves as smoking daily for at least a year.

Fortunately, there is another indicator of the health effects of smoking that reflects the many dimensions of smoking: the death rate from lung cancer. As noted above, smoking is the overwhelming risk factor in death from lung cancer, with 90% of male and 84-85% of female lung cancer deaths in the US attributable to smoking (Oza et al., 2011). Because of the cumulative and delayed impact of smoking on lung cancer mortality, lung cancer exhibits prominent “cohort effects”; rates of death from lung

¹ Soneji and King (2012) incorporate data on smoking and obesity into their Bayesian projections of future mortality in the US, but “do not attempt to estimate causal effects of specific risk factors” (p. 1046). See also King and Soneji (2011).

cancer are more predictably arrayed by birth cohort rather than by period (Janssen & Kunst, 2005; S. Preston & Wang, 2006; Willets, 2011; Yamaguchi, Mochizuki-Kobayashi, & Utsunomiya, 2000). Figure 1.1A shows male death rates from lung cancer in the United States in various birth cohorts. Clearly, there is a near parallelism among these rates on a log scale, implying that the sequence of death rates for one cohort is nearly a constant multiple of the death rates for another cohort. Figure 1.1B shows that this parallelism is missing when data are arrayed by period rather than by cohort.

Our estimates of the mortality effects of changes in smoking are based on the identification of cohort effects in lung cancer mortality. Mortality levels that are unique to cohorts are obviously a convenient vehicle for projecting mortality because cohorts age with completely predictable regularity. A second stage in the estimation of the effect of changes in smoking patterns is to translate projected changes in lung cancer mortality into changes in all-cause mortality.

Data

Data on lung cancer deaths by age, sex, and period are drawn from annual volumes of Vital Statistics of United States for periods from 1940 through 1949, from the website of the World Health Organization/International Agency for Research on Cancer for 1950 through 1998, and from files of Underlying Cause of Death 1999-2009 on CDC WONDER Online Database for 1999-2009 (National Center for Health Statistics, 2012). In this paper, lung cancer refers to cancer of lung, bronchus, trachea and pleura. The International Classification of Diseases (ICD) was used to identify lung cancer deaths.

The entire study period of 65 years from 1945 to 2009 are covered by ICD from version 5 to version 10. The corresponding ICD version codes used for each individual time period are list in the table below.

Year (ICD Version)	ICD Codes
1939-1948 (ICD-5)	47b-47f
1949-1957 (ICD-6)	162, 163
1958-1967 (ICD-7A)	162, 163
1968-1978 (ICD-8A)	162
1979-1998 (ICD-9)	162
1999-2009 (ICD-10)	C33, C34

Estimates of population size and counts of deaths from all causes combined are taken from the Human Mortality Database for 1933-2007. These data for 2008 and 2009 are drawn from National Center for Health Statistics (2012).²

Data on smoking by cohort are based on a detailed reconstruction of smoking histories by Burns et al. (1998). They employed a total of 15 National Health Interview

² Estimates pertaining to birth cohorts are created by organizing a data matrix in 5-year age groups and 5-year time blocs. In order to align cohort mortality data with cohort smoking data, we defined 5-year birth cohorts that were centered on birth years 1900-04, 1905-09, etc. For example, mortality rates in the birth cohort of 1905-09 were comprised of death rates at ages 40-44 in 1947-51, death rates at ages 45-49 in 1952-56, and so on. The final mortality observations for cohorts still alive consisted of death rates in 2007-09.

Surveys (NHIS) conducted between 1965 and 1991 to estimate cohort smoking histories. David Burns supplied us with unpublished estimates using the same methodology that incorporated data from three additional National Health Interview Surveys through 2001 (Burns et al., 1998). We updated the series using NHIS data through 2009. We converted these data into an estimate of the average number of years spent as a current smoker before age 40. This value is derived by summing across ages between 0 and 39 the annual proportion of cohort members who were estimated to be current cigarette smokers.

For cohorts that had not reached age 40 in 2010, we estimate the future cumulative years of smoking by age 40 based on observed cumulative years smoked at younger ages. For this purpose, we use regressions predicting the mean cumulative years of smoking by age 40 with independent variables representing cumulative smoking indexes by age 35, by age 30, by age 25, and by age 20. We add a sex indicator and a trend variable to the regressions. Regressions are estimated on data for the 16 cohorts for which we have complete data up to age 40. The regressions in all cases explain at least 97% of the variance in cumulative years of smoking before age 40. For the two cohorts born after 1990, we fix the variable at its level estimated for the 1985-90 cohort. The resulting series are presented in Figure 1.2.

Methods

Methods for projecting the mortality effects of smoking

Our initial goal is to identify how lung cancer mortality varies from cohort to cohort so that we can project these cohort effects into the future. We try two principal

ways to estimate cohort effects. One is to relate lung cancer mortality to a cohort smoking variable that had proven useful in prior research on all-cause mortality (S. Preston & Wang, 2006; H. Wang & Preston, 2009). As noted, that variable is the mean cumulative number of years that a member of a cohort had smoked prior to age 40, designated S^c for cohort c . For each sex, we estimate an equation of the form

$$\ln(M_a^c) = A + \beta_a X_a + \beta_s \ln(S^c) + \varepsilon \quad (1)$$

where M_a^c is the lung cancer death rate at age a in cohort c , X_a is an indicator of age category a , β_a is the coefficient of age category X_a , and β_s is the coefficient of $\ln(S^c)$. We estimate this model using negative binomial regression on death counts on all observations at ages 40-44 to 80-84 for periods beginning in 1947-51. This starting period was chosen because it produced the best fit to actual death rates in 2009 among all potential start years from 1937 to 1987. The coefficients of $\ln(S^c)$ are 1.279 for males and 0.929 for females. Greater sensitivity of males than females to their respective smoking histories was also found by Wang and Preston (2006) and Preston and Wang (2009) based on all-cause mortality. It is also a common finding in prospective cohort studies, perhaps because women smokers on average consume fewer cigarettes per day, inhale less frequently, and smoke cigarettes lower in tar content (Thun et al., 1997) Age coefficients are monotonically and smoothly rising at a diminishing rate for both sexes.

The second approach is to estimate “cohort effects” as coefficients of dummy variables pertaining to various cohorts, without any reference to smoking histories.³

³ Such an estimate could be made using an age/period/cohort model, but it is widely recognized that introducing age, cohort, and period variables into the same model creates an identification problem because

Using negative binomial regression on death counts, we estimate the parameters of a straightforward age/cohort model,

$$\ln(M_a^c) = A + \beta_a X_a + \beta_c X_c + \varepsilon , \quad (2)$$

where M_a^c is the lung cancer death rate in cohort c at age a , β_a and β_c are the coefficients of age category a and cohort c and X_a and X_c are indicators of age and cohort membership.

Figures 1.2A and 1.2B plot cohort effects estimated from equation (2) and the mean number of years of smoking before age 40 for each cohort, used to estimate equation (1). The two series for women obviously track one another closely for both sexes, including a bump for female cohorts born 1955-64. For men, both series are hill-shaped, although the peak of the smoking series occurs earlier than the peak cohort coefficient. Figure 1.2 illustrates that cohort effects in lung cancer are dominated by smoking histories.

Our projections are based on equation (1), which uses the smoking series. A main advantage of this approach is that we are able to observe smoking behavior for cohorts as young as age 15-19. In contrast, the cohort coefficients from equation (2) are not robustly estimated until a cohort has reached the 40's, when substantial numbers begin to die from lung cancer. Furthermore, the smoking-based analysis produces predicted death rates in

of the perfect linear association between any two of these variables and the third (Fienberg & Mason, 1978). Our efforts to introduce period measures into an age/cohort model were unsuccessful in the sense that they resulted in implausible cohort and period effects, presumably because of these colinearity issues. A second reason for not invoking an age/period/cohort model is that we had no strong hypothesis about period effects on lung cancer mortality, since we considered such mortality to be primarily a function of cohort smoking histories.

2009 that are much closer to the actual death rates in that year than the analysis using cohort coefficients, which underestimate mortality significantly for older cohorts.

We test the predictive validity of Model (1) by estimating the parameters of the model on data through 1995-99 and using the age and cohort coefficients to project mortality in 2005-09. Comparing the projected mortality level to the actual level in the prime ages of 50-84, the mean error in projected rates is 1.54% for males and 1.17% for females. The mean absolute error is 4.64% for males and 5.64% for females. A prediction of “no change” between 1995-99 and 2005-09 produces a mean error of -28.23% for males (i.e., an overprediction) and -9.65% for females. The mean absolute errors for a no-change prediction are 28.23% for males and 14.36% for females. These are obviously many times greater than errors produced by our model, which performs well in predicting changes in lung cancer mortality between 1995-99 and 2005-09. We conclude that our model proves effective in out-of-sample prediction. It is worth noting that, at these ages, a 10% error in all age-specific death rates would produce an error of less than 3% in life expectancy (Keyfitz & Golini, 1975).

Translating changes in lung cancer mortality into changes in all-cause mortality

Although lung cancer mortality serves as an excellent marker of the health effects of smoking, lung cancer does not account for a majority of deaths attributable to smoking. Cardiovascular diseases, other cancers, and chronic obstructive pulmonary diseases (COPD, which includes bronchitis and emphysema) also make large contributions. Two methods have been developed to connect smoking-related mortality

from lung cancer to smoking-related mortality from other causes of death. Peto et al. (1992) convert observed lung cancer death rates into an estimate of smoking “prevalence” by referring to the difference between lung cancer death rates for smokers and non-smokers in Cancer Prevention Study II (CPS-II) (Peto, Lopez, Boreham, Thun, & Heath, 1992). This estimate of smoking prevalence is then used to estimate the risk attributable to smoking for other smoking-related causes of death by employing the cause-specific relative risks for smokers versus non-smokers from CPS-II.

The second method also uses lung cancer mortality as the basic indicator of the damage caused by smoking (S. Preston, Glej, & Wilmoth, 2010, 2011). However, rather than relying on the relative risks from CPS-II or any other study, it estimates the macro-level statistical association between lung cancer mortality and mortality from all other causes of death in a dataset of 21 countries covering the period 1950 to 2006, including 9.9 billion person-years of exposure and 284 million deaths. In addition to lung cancer mortality, the statistical model includes age, sex, period, and country effects as well as interactions among them. This approach is motivated by the expectation that lung cancer mortality is a reliable indicator of the damage from smoking and that such damage has left a sufficiently vivid imprint on other causes of death that it is identifiable in country-level data. The strong statistical relations that emerge are consistent with that expectation.

The two methods of translating lung cancer mortality into all-cause mortality give very similar results. The proportion of deaths attributable to smoking that are estimated by the two methods is correlated at 0.96 for males and 0.94 for females across 20 countries in 2000 (S. Preston et al., 2011). Both methods implicitly assume that the pattern of lags between smoking and lung cancer death is similar to that between smoking

and other causes of death. Is that assumption reasonable? Preston, Glej, and Wilmoth (2011) (PGW) experimented with various lags between lung cancer mortality and mortality from other causes of death and found that a model in which the two death rates were contemporaneous (i.e., exhibited no lags) worked best (unpublished result). Oza et al. (2011) examine time-patterns of relative mortality risks of smokers from various causes of death. Relative to the lag between smoking behavior and death for lung cancer, they found the lag structure to be longer for chronic obstructive pulmonary disease (COPD) and shorter for cardiovascular diseases. Using the Peto et al. (1992) approach, the estimated number of deaths attributable to smoking differed by only 1.7% when lag structures were incorporated compared to when they weren't. Thus, it appears that the pattern of lung cancer lags is sufficiently similar to that for the aggregate of other causes of death that serious distortions do not arise from assuming that they are, on average, the same.

To translate projected lung cancer death rates into death rates from all causes, we use the set of translation factors by age and sex drawn from Preston, Glej, and Wilmoth (2011).⁴ Below, we explore the sensitivity of results to this choice of translation factors.

Uncertainty analysis

We analyze uncertainty in our estimates of the effects of smoking on change in life expectancy using a bootstrapping procedure (Efron & Tibshirani, 1986). We

⁴ Preston, Glej, and Wilmoth do not estimate coefficients for ages below 50. We assume that the coefficients for ages 50-54 apply to ages 40-49. Since coefficients decline with age, this choice probably produces an underestimate of smoking-attributable deaths, but there are very few deaths in the age interval 40-49, so results are scarcely affected by this assumption.

generate 1000 sets of bootstrapped coefficients for the lung cancer mortality and PGW models. We then apply the 1000 sets of age-specific lung cancer mortality rates to the 1000 sets of PGW coefficients to calculate mortality from all causes and life expectancies at age 40. The 2.5 and 97.5 percentile values from the simulated life expectancy estimates are extracted as the 95% confidence interval.

Results

Figure 1.3 presents the results of this analysis. Male age-specific death rates are expected to decline at every age throughout the projection period. The heaviest smoking male cohorts are already aged 80+ in 2010 and the impact of persistent declines in smoking from cohort to cohort is to produce a steady decline in relative death rates as time advance. In contrast, female rates are expected to rise in the oldest age intervals during the early years as heavier-smoking cohorts replace lighter-smoking ones (cf. Figure 1.4). Projected male declines are larger than female declines in nearly all comparisons, reflecting the more gradual changes in cohort smoking propensities among women.

Table 1.1 converts the age-specific projections of mortality change into estimates of the effect on life expectancy at age 40. Males show a relatively steady improvement in life expectancy from smoking reductions and a total gain of 1.52 years by 2040. In contrast, female life expectancy is expected to fall from changing smoking patterns between 2010 and 2015 as the heaviest smoking cohorts continue moving into the prime ages of dying. There is projected to be virtually no gain in female life expectancy as a

result of smoking reductions between 2010 and 2020. However, female gains accelerate after 2025 as the heaviest smoking cohorts begin to disappear. By 2040, women are projected to have gained 0.85 years in $e(40)$ from smoking reductions.

Two other projections have been made of anticipated changes in mortality as a result of changing smoking patterns. Wang and Preston (2009) add a cohort smoking term to the conventional Lee-Carter model of mortality change from all causes of death combined. They summarize their results in the form not of life expectancy but rather of the probability of surviving from age 50 to age 85. For the projection period 2009-2034, they estimate that reductions in smoking will increase the probability of male survival by 15.8% and of female survival by 7.2%. In the present set of projections, changes in this probability between 2010 and 2035 are 13.4% for males and 4.7% for females. The proportion of lung cancer deaths attributable to smoking is in the range of 85-90% (Oza et al., 2011), whereas the proportion of all-cause deaths attributable to smoking is in the neighborhood of 20% (Mokdad et al., 2004, 2005). Accordingly, mortality from lung cancer is a much more sensitive indicator of the damage from smoking than is all-cause mortality. As a result, we believe the present estimates are more reliable.

Stewart et al. (2009) also project the effects of changes in smoking on future life expectancy by extrapolating trends in smoking distributions and applying death rates by smoking status from NHANES (Stewart, Cutler, & Rosen, 2009). They do not differentiate between the sexes. They estimate that, in a 15-year projection period beginning in 2005, declines in smoking will produce a 0.31 year gain in life expectancy at age 18. In our 15-year projection beginning in 2010, we estimate that declines in smoking will raise life expectancy at age 40 by 0.80 years for males and 0.15 years for females,

with an average gain of 0.47 years.⁵ While our results appear to show a faster improvement than theirs, the rate of improvement accelerates through the period. In our 10-year projection ending in 2020, the same year that the Stewart et al. projections end, our gain in life expectancy (mean, males and females) is 0.28 years compared to their 0.31 years over the preceding 15-year period. Thus, our results appear reasonably consistent with theirs over this short projection period.

Sensitivity Analyses

We performed sensitivity analyses of the effect of changes in procedures on outcomes, by estimating the effect of an alternative procedure on age-specific death rates and converted those rates into estimated effects on life expectancy at age 40. Results for life expectancy at age 40 are shown in Table 1.2. The values in that table are the difference between the life expectancy value produced by the alternative procedure and that produced by our main procedures. A positive value means that the alternative procedure resulted in a gain in projected life expectancy relative to the main procedure.

The sensitivity analysis uses an alternative set of relations between lung cancer mortality and all-cause mortality. The main results presented above are based on relations estimated across 21 countries from 1950 to 2006. Fenelon and Preston (2012) instead estimate coefficients relating lung cancer to all-cause mortality that are based on variations across 50 states of the US between 1996 and 2004 (Fenelon & Preston, 2012). Coefficients that predict mortality from other causes of death on the basis of lung cancer

⁵ Changes in life expectancy at ages 18 and 40 are highly comparable because so few years of life are lost between these ages.

mortality are very similar for men to those in Preston, Gleib, and Wilmoth (2011) but they are lower for women at younger ages.⁶

Results in Table 1.2 show that the sensitivity of results is minor for the first 10 years of projection, modest for the second 10 years, and sizeable by 2040. Of the projected 1.52 years of gain in life expectancy from reductions in smoking by 2040 for males in Table 1.1, 0.32 years would be eliminated if the alternative relations were used. Of the 0.85 year gain for women, 0.36 years is eliminated if the alternative relations are used. The alternative results have the virtue of being based on contemporary relations in the US, but the main results are based on many more data points. We believe that the comparison of the two approaches provides a realistic picture of the degree of uncertainty in the smoking results. However, using either the main approach or the alternative, declines in smoking are expected to produce substantial gains in life expectancy by 2040.

Conclusion

The effects of past and future changes in smoking are likely to result in an overall improvement in US life expectancy over the next 30 years. This improvement occurs mainly because the advantages of reductions in smoking. Over the next decade, however, the effect of smoking is likely to produce only a very small improvement in mortality for women because the heaviest smoking cohorts of American women are still in or

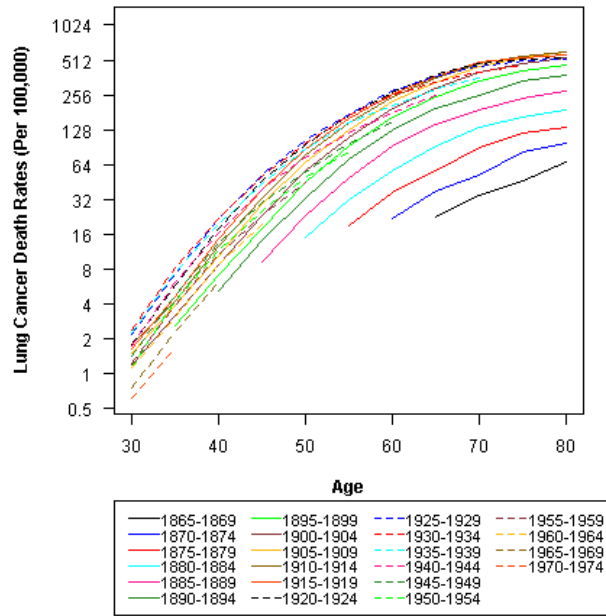
⁶ Neither approach estimated a coefficient for ages 85+. Preston, Gleib, and Wilmoth (2011), the source of the main analysis, used the mean coefficient at ages 70-74, 75-79, and 80-84 to apply to ages 85+. We make this same assumption for the alternative method based on Fenelon and Preston (2012).

approaching the ages of greatest vulnerability to death. Our results appear to be in reasonable accord with those of Stewart et al. (2009) over their shorter projection period.

Are the changes that we have projected large or small? One useful metric is provided by projections made by the Social Security Administration (Bell and Miller 2005). They anticipate that life expectancy at age 40 will grow between 2010 and 2040 by 2.55 years for men and 2.17 years for women, somewhat smaller gains than forecast by most other analysts (Wilmoth, 2005). Relative to projections by the Social Security Administration, the mean of male and females gains that we estimate from reduced smoking (1.54 years among men and 0.85 year among women) would themselves account for almost exactly half of the projected mean gain in life expectancy. Smoking clearly exerts a major influence on American mortality and warrant continued monitoring and analysis.

Figure 1.1: U.S. Lung Cancer Mortality for Males

A. By Cohort



B. By Period

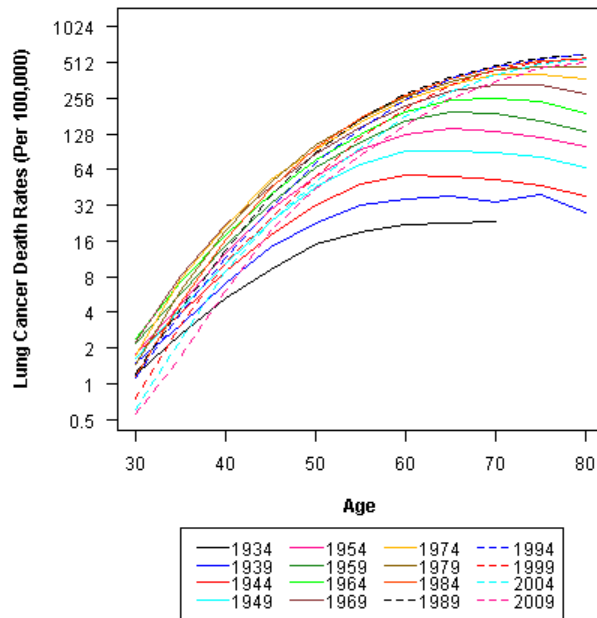
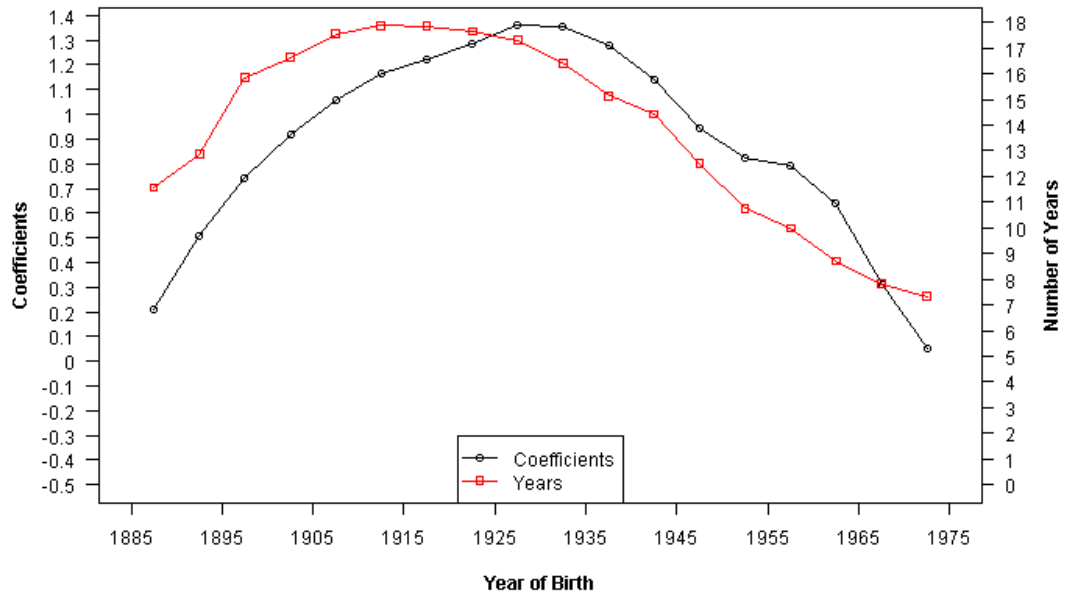


Figure 1.2: Cohort Coefficients Predicting Lung Cancer Mortality and Cumulative Cohort Smoking by Age 40

A. Males



B. Females

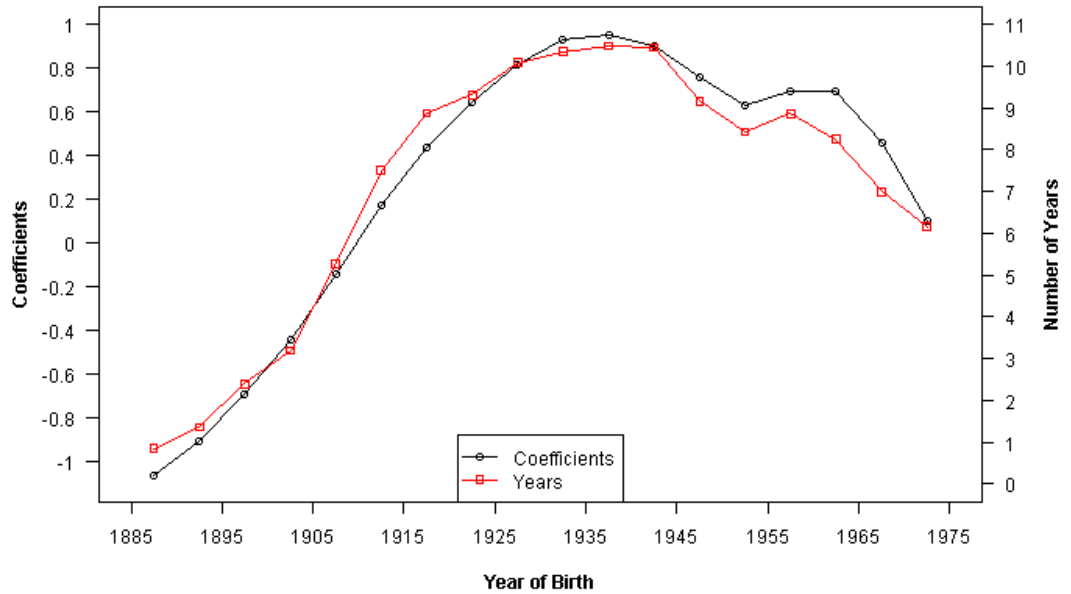
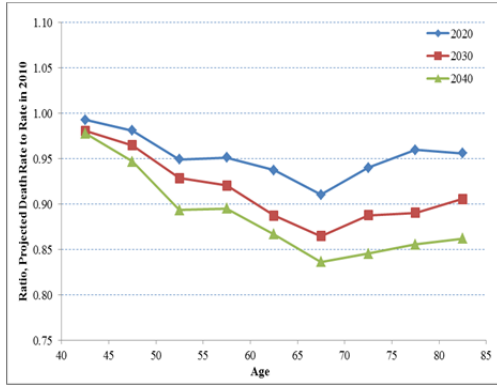


Figure 1.3:: Effects of Projected Trends in Smoking on Age-Specific Death Rates

Males



Females

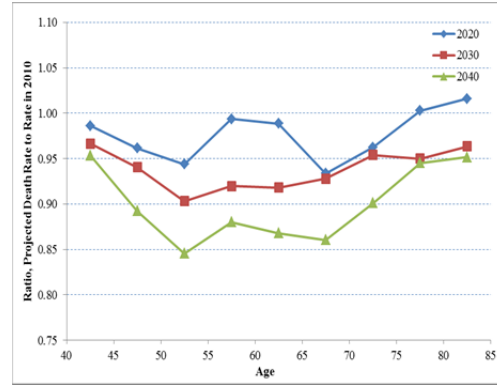


Figure 1.4: Mean Number of Years Spent as a Cigarette Smoker before Age 40 by Cohort

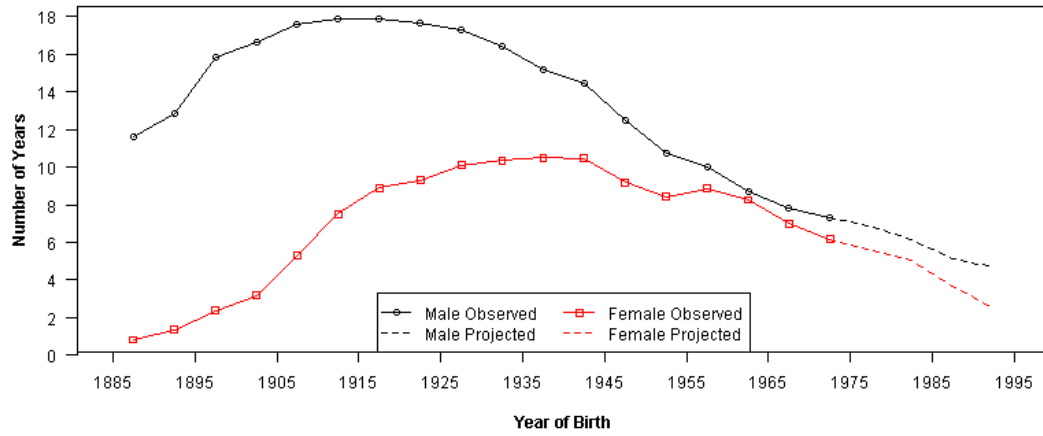


Table 1.1: Changes in Life Expectancy at Age 40

Year	Male	Female
2015	0.26 (0.07, 0.47)	-0.03 (-0.52, 0.46)
2020	0.54 (0.33, 0.76)	0.04 (-0.44, 0.53)
2025	0.81 (0.58, 1.08)	0.15 (-0.33, 0.63)
2030	1.05 (0.78, 1.35)	0.32 (-0.15, 0.81)
2035	1.31 (1.00, 1.67)	0.62 (0.20, 1.13)
2040	1.54 (1.18, 1.94)	0.85 (0.41, 1.38)

Table 1.2: Sensitivity of Results to Changes in Procedures

Year	Male	Female
2020	-0.067	0.012
2030	-0.173	-0.107
2040	-0.322	-0.360

A positive value means that the alternative procedure resulted in a gain in projected life expectancy relative to the main procedure

Chapter 2 Forecasting the Healthy Life Expectancy among Older Adults in the US Using Cohort Smoking and Obesity History

Introduction

Life expectancy (LE) in the United States has experienced gradual increases over the past decades, reaching historic highs of 76.2 years for men and 81.0 years for women in 2010 (Murphy, Xu, & Kochanek, 2013). This mortality fall is primarily a result of health care improvements and lifestyle changes, among which reduction in smoking is a leading cause. Nearly 800,000 lung cancer deaths in the US were prevented due to the decline in smoking between 1975 and 2000 (Moolgavkar et al., 2012). However, obesity, (particularly Class II/III obesity) is thought to be responsible for an increasing proportion of deaths, as its prevalence has been growing in recent years (K M Flegal, Carroll, Kuczmarski, & Johnson, 1998; Mokdad et al., 2004; Ogden, Carroll, Kit, & Flegal, 2012; Peeters et al., 2003; Y. Wang & Beydoun, 2007). The current trends of both smoking and obesity are expected to continue, so are the trends of deaths associated with these two factors (S. H. Preston, Stokes, Mehta, & Cao, 2014).

Despite its popularity as a summary indicator of mortality, life expectancy alone is not sufficient to measure the quality of population health. Whether the fall in mortality is accompanied by a fall in disability is also of great interest in health studies. Just like mortality, disability is also affected by health behaviors. At the individual level, smoking and obesity are found to be associated with both higher rates and longer duration of

disability among older adults in the US (Jenkins, 2004; Reynolds & McIlvane, 2009; Reynolds, Saito, & Crimmins, 2005; U.S. Department of Health and Human Services, 2014; Walls, Backholer, Proietto, & McNeil, 2012). This is primarily because smokers and obese individuals have a higher chance of suffering from many chronic diseases, particularly lung cancer, cardiovascular diseases, and diabetes (Al Mamun et al., 2004; Al Snih et al., 2007; Gregg et al., 2005; P. N. Lee, Forey, & Coombs, 2012; Mokdad et al., 2003). However, at the population level, the degree of disability (often summarized by the prevalence of disability) is influenced by many factors. Not only increase in disability incidence or decline in disability recovery, but also increase in survival rates of the disabled or of those who may become disabled later in life could lead to higher prevalence of disability. To summarize the impacts of the interplay of morbidity and mortality on population health, healthy life expectancy is often calculated using combined mortality and morbidity information (Robine, Romieu, & Michel, 2003). The most common forms used for measuring healthy life expectancy are disability-free life expectancy (LE^{ND}) and life expectancy with disability (LE^D), respectively defined as the average number of years one is expected to live without and with disability. In addition, the proportion of years living without disability (LE^{ND} / LE) can be used as a relative measure for morbidity.

Three major hypotheses about the evolution of the population's morbidity over time have been developed. The "compression of morbidity" hypothesis argues that effectively postponing the onset of chronic disease and consequent disability will create a decrease in the number of years spent with disability (Fries, 1980). In contrast, Olshansky et al. (1991) proposes a "expansion of morbidity" hypothesis that claims the gain in life

expectancy is primarily due to keeping those who suffer from chronic diseases alive in a disabled state, and therefore not necessarily accompanied by more years of disability-free life expectancy (Olshansky, Rudberg, Carnes, Cassel, & Brody, 1991). The “dynamic equilibrium” hypothesis states that although increase in total life expectancy is likely to be a result of increase in both LE^{ND} and LE^D , the number of years spent with severe morbidity is prone to remain stable (K. G. Manton, 1982).

In order to understand which of the three hypotheses best describes the actual past experience of the older adults in the US, one needs to study the past mortality and morbidity trends of the population during the observed period as well as the underlying epidemiological transitions that drive these trends. Throughout the 20th century, the prevalence of cigarette smoking in the US can be best described as an inverse U-shaped curve, in the presence of sex difference (Centers for Disease Control and Prevention (CDC), 2005; S. H. Preston et al., 2014). Although the population is smoking less, there is no consensus in the literature on whether this change is leading to fewer years spent with disability. Some studies claim that smoking is associated with both smaller LE^{ND} and smaller LE^D , leaving never-smokers the same or even more years with disability (Al Mamun et al., 2004; Ferrucci et al., 1999; Klijs, Mackenbach, & Kunst, 2011; Reuser, Bonneux, & Willekens, 2009; Van Oyen et al., 2014). In contrast, other studies support the hypothesis that smokers are subject to expansion of disability in both absolute and relative terms, despite their already relatively shorter life (Brønnum-Hansen & Juel, 2001; Hubert, Bloch, Oehlert, & Fries, 2002; Nusselder, Looman, Marang-van de Mheen, van de Mheen, & Mackenbach, 2000). The discrepancy between the above conclusions

lies primarily in whether the mortality or disability associated with smoking contributes more to the difference in LE^{ND} and LE^D based on smoking status.

On the other hand, obesity is associated with many conditions that are disabling but not fatal, including osteoarthritis and back pain that limit mobility and daily activities (Sach et al., 2007; Stürmer, Günther, & Brenner, 2000). In addition, the mortality risks of obesity-related chronic diseases, such as cardiovascular diseases, strokes and diabetes, have declined over the last two decades as a result of improvement in medical intervention and prevention (Gregg et al., 2005; N. K. Mehta & Chang, 2011; NCCDHP-CDC, 1999). This further extends life spent with disability for the obese individuals. Many studies accordingly conclude that obesity may have stronger impact on disability than mortality and creates extra burden for health care (Al Snih et al., 2007; Must et al., 1999; Reuser et al., 2009; Reynolds et al., 2005).

The cohort patterns of the impact of smoking and obesity on health have been recognized by many existing studies (Masters et al., 2013; Peeters et al., 2003; S. Preston & Wang, 2006). Hence, these are valuable information that can be applied to forecasting future health outcome of the population. The prevalence of obesity is projected to continue the current rising trend, while the prevalence of smoking is expected to keep falling in the US over the next few decades (E. a Finkelstein et al., 2012; Ruhm, 2007; Stewart et al., 2009). Given that smoking and obesity affect mortality and morbidity differently, their trends combined have important implications for population health in the future. Although abundant studies have forecasted future mortality, few have attempted to do so for future morbidity. To date, there have been only two studies that

forecast the healthy life expectancy, among which only one is an application to the US population, and none of them accounts for the underlying factors that drives mortality and morbidity (Majer, Stevens, Nusselder, Mackenbach, & van Baal, 2013; K. Manton, Gu, & Lamb, 2006). As Wang and Preston (2009) show, including a smoking covariate substantially reduces the anomalies in the shape and sex differences for parameter estimates which may otherwise be severely distorted as the projection period extends further.

The present study aims to contribute to the literature by producing projections of both LE^{ND} and LE^D for the US population at age 55 in associations with its observed history of health behaviors at younger ages. A multi-state life table (MSLT) approach proposed by Majer et al. (2013) is applied to estimate the transition rates among different health status. A modified Lee-Carter model that incorporates cohort smoking and obesity history will then be used to fit and forecast the obtained transition rates, based on which LE^{ND} and LE^D will be calculated.

Data

The information for disability, smoking and obesity is obtained from the Integrated Health Interview Series (IHIS), which maintains a harmonized set of the public use data and documentation of the US National Health Interview Survey (NHIS) (Minnesota Population Center and State Health Access Data Assistance Center, 2012). NHIS is a nationally representative cross-sectional survey of US non-institutionalized

civilians, and is conducted annually by the National Center for Health Statistics. It collects comprehensive information about demographic, social-economic status, general health, health-related behaviors and activity limitations. The sample used in this study contains observations that are 55 years old and above in survey years from 1982 to 2010.

The disability variable is constructed using questions that ask individuals' limitations in activities due to chronic conditions. For surveys from 1982 to 1996, four categories are available, including *not able to perform major activities, limited in amount/kind of major activities, limited in other activities* and *not limited*. However, there are only three categories for surveys after 1996, including *limited in any way, not limited in any way* and *unknown*. In order to make the disability status comparable across surveys, an individual is considered to be disabled if he/she reports any limitations of activities at all.

The smoking history by 5-year gender-specific birth cohort (e.g. 1885-1889, 1890-1894) is reconstructed based on the data in Burns et al. (1998). Their original cohort smoking history is estimated using 15 NHIS between 1965 and 1991 (Burns et al., 1998). This data is further updated by Preston et al. (2014) using additional NHIS surveys through 2009 and converted into an estimate of the average number of years a cohort had smoked prior to age 40 (S. H. Preston et al., 2014).

Similarly, the variable for obesity is constructed in a cohort fashion as well. I compute the obesity prevalence at age 40 for each 5-year birth cohort by sex using NHIS data. Obesity is defined as having a Body Mass Index (BMI) that is over 30.

In order to extrapolate the mean cumulative years of smoking by age 40 for cohorts that are still below 40 years old by 2010, I regress a cohort's mean cumulative years of smoking by age 40 on the observed mean cumulative years of smoking by age 35, by age 30, and by age 25 for the cohorts for which this information is all available. Similarly, I regress a cohort's prevalence of obesity at age 40 on the observed prevalence at age 35, at age 30 and at age 25 for those cohorts that have complete BMI information up to age 40. Dummy variables for sex and birth cohorts are added to these regressions. For smoking, the above models explain at least 97% of the variance in the dependent variable in all cases. For obesity, over 92% of the variance is explained. I then estimate the corresponding values for the smoking and obesity variables based on the coefficients estimated in the regression models. Because the end of the forecast period is 2040, the youngest cohort that requires extrapolation for the smoking and obesity variables are born in 1985-1989 and will reach 55 years old by 2040. However, the obesity variable also needs to be extrapolated back for cohorts born before 1935, as body weight information is collected only after 1976. I only extrapolate this variable back to cohorts born in 1920-1924 and fix it at this level for cohorts born prior to 1920.

In order to estimate the transition rates between different health states using a multi-state life table, population-level age- and gender- specific mortality data is also needed. The Human Mortality Database (HMD) is used for this purpose. Mortality rates are drawn from the HMD for age 55 and above for the observation period (1982-2010).

Methods

Estimation of the Transition Rates

Three health states (non-disabled, disabled, dead) are considered in this study. Given this, there are four possible types of transitions: a healthy person may experience onset of disability or may die; and a disabled person may recover or may die. As Guillot and Yu (2009) and Majer et al. (2013) both point out, the prevalence of disability for a cohort aged $x+1$ at time $t+1$ is a function of the following: prevalence of disability for the same cohort when it was aged x at time t , the probability of disability onset and recovery, as well as the probability of death for both non-disabled and disabled during this one-year time interval (Guillot & Yu, 2009; Majer et al., 2013). This can be expressed by the equation below.

$$\pi_{x+1,t+1}^U = \frac{\pi_{x,t}^U (1 - q_{x,t}^{UD} - q_{x,t}^{UH}) + (1 - \pi_{x,t}^U) q_{x,t}^{HU}}{1 - (1 - \pi_{x,t}^U) q_{x,t}^{HD} - \pi_{x,t}^U q_{x,t}^{UD}} \quad (1)$$

where $\pi_{x+1,t+1}^U$ and $\pi_{x,t}^U$ are the corresponding prevalence of disability for a cohort aged $x+1$ at time $t+1$ and for the same cohort exactly a year ago. These prevalence rates are estimated using NHIS surveys conducted in two consecutive years, using NHIS sample weights to account for non-responses and make prevalence rates representative for the US non-institutionalized population.

$q_{x,t}^{HD}$ and $q_{x,t}^{UD}$ respectively denote the probability that non-disabled and disabled individuals aged x at time t will die between time t and $t+1$. These probabilities can be separately derived from the mortality rates of non-disabled and disabled, as shown in the

Appendix 1. However, no separate age-specific mortality rates are available for disabled and non-disabled, because of the lack of a longitudinal dataset that is large enough to provide reliable estimates for multiple age groups in a long period, as needed for the forecasting purpose in this study. Therefore I take advantage of the following inter-relationship among overall mortality ($m_{x,t}$), state-specific mortality ($m_{x,t}^{HD}$ and $m_{x,t}^{UD}$), relative mortality risk of disabled ($HR_{x,t}$), and prevalence of disability ($\pi_{x,t}^U$) to derive separate mortality rates for disabled and non-disabled:

$$m_{x,t}^{UD} = m_{x,t}^{HD} HR_{x,t} \quad (2)$$

$$\text{and } m_{x,t}^{HD} = \frac{m_{x,t}}{HR_{x,t} \times \pi_{x,t}^U + (1 - \pi_{x,t}^U)} \quad (3)$$

The only unknown in equation (3) is the hazard ratio of disabled. This is estimated using individual-level data from NHIS conducted in 1986-2004, during which period each participant in the survey is linked to death certificate data found in the National Death Index (NDI). A Cox proportional hazard model with left truncation is fitted by sex, and no significant age or year interaction is found (Cox, 1972). Consequently, I assume the estimated hazard ratios, 2.10 (95% CI: 2.07-2.13) for men and 2.02 (95% CI: 1.99-2.05) for women, are constant over time and age.

Now only the probability of disability onset ($q_{x,t}^{HU}$) and the probability of recovery from disability ($q_{x,t}^{HU}$) in equation (1) are left unsolved. For simplicity of modeling and to obtain more robust forecast, I assume the recovery from disability is absent, as practiced in Majer et al. (2013). As a result, the transition from non-disabled to disabled can be

considered as the net incidence of disability, and equation (1) can be re-written as below and can be used to derive the only unknown $q_{x,t}^{HU}$:

$$\pi_{x+1,t+1}^U = \frac{\pi_{x,t}^U (1 - q_{x,t}^{UD}) + (1 - \pi_{x,t}^U) q_{x,t}^{HU}}{1 - (1 - \pi_{x,t}^U) q_{x,t}^{HD} - \pi_{x,t}^U q_{x,t}^{UD}} \quad (4)$$

Modeling and Forecasting the Transition Rates

Once the probability of non-disabled becoming disabled ($q_{x,t}^{HU}$) in equation (4) is estimated, it can be converted to transition rates $m_{x,t}^{HU}$ (see Appendix 1). I assume the variations in transition rates for both mortality and disability can be partially explained by age and period, as argued by Lee and Carter (R. D. Lee & Carter, 1992). The portion, except for the residual, that is left unexplained by age and period is considered to be influenced by the history of smoking and obesity (H. Wang & Preston, 2009).

Accordingly, I use the Lee-Carter model that incorporates cohort smoking and obesity history to fit and forecast all three types of transition rates. Given that the two leading risk factors, smoking and obesity, of mortality and morbidity are adjusted for, the same temporal trend in both mortality and morbidity is assumed for both sexes (H. Wang & Preston, 2009). The model can be expressed as:

$$\ln m_{x,t}^{g,i} = \alpha_x^{g,i} + \beta_x^{g,i} \kappa_t^i + \theta^{g,i} S_{t-x}^g + \lambda^{g,i} O_{t-x}^g + \varepsilon_{x,t}^{g,i} \quad (5)$$

where g specifies gender and i specifies the three types of transition: non-disabled to disabled (HU), non-disabled to death (HD) and disabled to death (UD). The parameter α_x is the average of the log transition rate at age x over time, κ_t quantifies the underlying

development of transition rates over time and is assumed to be the same for men and women when smoking and obesity are adjusted for. β_x is the changes in transition rates at age x in response to changes in κ_t over time. S_{t-x} and O_{t-x} are respectively cohort history of smoking and obesity for a cohort born in year $t-x$, and θ and λ are corresponding coefficients that measure the effect of smoking and obesity on the specific transition rates. The cohort smoking history is measured by the average number of years that members from a birth cohort smoked prior to age 40. The cohort obesity history is measured by the prevalence of obesity (BMI \geq 30) at age 40 for a birth cohort.

The parameters are estimated by minimizing the sum of squared errors of the singular value decomposition performed for both sexes combined, as specified by the following equation (H. Wang & Preston, 2009):

$$\begin{bmatrix} \ln m_{x,t}^{M,i} - \theta^{M,i} S_{t-x}^M - \lambda^{M,i} O_{t-x}^M \\ \ln m_{x,t}^{F,i} - \theta^{F,i} S_{t-x}^F - \lambda^{F,i} O_{t-x}^F \end{bmatrix} = \begin{bmatrix} \alpha_x^{M,i} \\ \alpha_x^{F,i} \end{bmatrix} + \kappa_t^i \begin{bmatrix} \beta_x^{M,i} \\ \beta_x^{F,i} \end{bmatrix} + \begin{bmatrix} \varepsilon_{x,t}^{M,i} \\ \varepsilon_{x,t}^{F,i} \end{bmatrix} \quad (6)$$

In order to find a model that best fits the actual transition rates, the model specified in equation (5) is tested using different sets of covariates. Specifically, the model is run with no covariates as the standard Lee-Carter model, with only cohort smoking history, with only cohort obesity history, with both cohort smoking and obesity history, and with both cohort smoking and obesity history as well as their interaction.

A few different specifications of ARIMA time series models are tested for forecasting κ_t for each type of transition. I found the random walk model with drift, ARIMA (0, 1, 0), yields reasonably good fit for all types of transitions and hence is used

to produce future values of κ_t for year 2011 to 2040. The variance-covariance matrix for κ_t of all three types of transitions is estimated to account for the future trends of these transitions jointly, and is used to produce 95% confidence intervals for the projected transition rates and life expectancy through simulation. In the simulation, the distribution of the disturbances is assumed to be an independently and identically distributed multivariate normal distribution, which has a mean of zero and a covariance matrix identical to the variance-covariance matrix discussed above.

Moreover, I use cohort-specific rather than period-specific measures of smoking and obesity, as making projections with the latter will require extrapolating the smoking and obesity variables for all ages for the entire forecasting period. On the other hand, only few cohort-specific measures need to be extrapolated since the data for most cohort behaviors are already available for the older population in this study. Specifically, people from the cohort born in 1970-1974 all reach age 40 by 2010, the last year of the observation period, and reach age 55 by 2025. And people from the cohort born in 1985-1989 will all reach age 55 by 2040, the last year of the forecasting period. Consequently, smoking and obesity variables need to be extrapolated for only three cohorts (1975-1979, 1980-1984 and 1985-1989). Then the future values of k , as well as corresponding cohort smoking and obesity history are used to estimate the future transition rates from 2011 to 2040, which are eventually translated into disability-free life expectancy (LE^{ND}) and life expectancy with disability (LE^D) using a multi-state life table approach described in the Appendix 1 (S. H. Preston, Heuveline, & Guillot, 2001). Because individuals aged 85 and above are top-coded in the NHIS surveys, the LE^{ND} and LE^D are estimated as partial life expectancies between age 55 and age 85.

Results

Figure 2.1 shows the disability prevalence for populations aged 55 to 64, aged 65 to 74, aged 75 to 84 and aged 85+ over time by gender. In general, the prevalence of disability increases with age. For those under 75 years old, disability prevalence has fallen over time for both sexes, although the decline has slowed down in recent years. This may well reflect the smoking decline and obesity epidemic among the younger cohorts. In contrast, the prevalence of disability has remained relatively constant over time for those 75 years and older. Additionally, the prevalence of disability for men and women below 75 years old are nearly identical throughout the observation period, while for those above 75 years old, women have higher disability prevalence. This is possibly because men born in the early cohorts tend to smoke more and thus are less likely to be disabled due to higher mortality.

Figure 2.2 plots the trends of smoking and obesity by cohort. We see a rise in the average cumulative years a cohort had smoked by age 40 for both men and women among the earlier born cohorts and a decline among the younger cohorts. The peak is reached for the male cohorts born in 1910-1920 and the female cohorts born in 1935-1945 respectively. In contrast, both sexes have experienced continuous increases in the prevalence of obesity at age 40, for cohorts born after 1925. The values of both smoking and obesity variables are extrapolated for the youngest cohorts, for whom data are not yet available. In general, the declining smoking trend for cohorts born after 1970 and the increasing obesity trend for cohorts born after 1965 are preserved for the youngest cohorts.

Figure 2.3 shows the trends of mortality and disability transitions over time by plotting the ratio of transition rates throughout the observation period (1982-2010) to those observed in 1982 at several ages (55, 65, 75 and 84). Because the relative risk of disability on mortality is assumed to be constant at all ages, the ratios for mortality of disabled and those for mortality of non-disabled are identical. Therefore, only the ratios for overall mortality are plotted. It is evident that men at all ages have experienced larger reductions in both mortality and disability than women during the entire observation period, reflecting men's earlier decline in smoking (Centers for Disease Control and Prevention (CDC), 2005; S. H. Preston et al., 2014; H. Wang & Preston, 2009).

Table 2.1 presents results from fitting the modified Lee-Carter models to the three types of transition rates with different sets of covariates for both sexes. Model 1 is simply a Lee-Carter model without any covariates. Model 2 includes cohort smoking history only, while Model 3 includes cohort obesity history only. In Model 4, both smoking and obesity covariates are included. Model 5 additionally includes an interaction term of smoking and obesity. Due to the constant assumption for the relative mortality risk of being disabled, the estimates for mortality of disabled and of non-disabled are the same for all models.

When I only adjust for smoking in the Lee-Carter model, a negative effect of smoking on survival is observed for both men and women, with the smoking risk for men being higher than that for women. This is consistent with existing literature that finds men are more responsive to the adverse effect of smoking than women (Chao et al., 2002; H. Wang & Preston, 2009). However, obesity is found to be associated with lower

mortality for both sexes (especially for men) when it is the only covariate included. As Figure 2.1 shows, the rise in cohort obesity prevalence is accompanied by the fall of cumulative smoking duration, to which the mortality decline in recent years is mainly attributed, particularly for men. Consequently, omitting smoking in the model leads to these counterintuitive estimates and smaller adjusted R-square in Model 3.

Adjusting for both covariates simultaneously to some extent reduces the confounding introduced by smoking. Since at the individual level smokers are on average leaner and less healthy, smoking decline tends to lead to higher obesity prevalence at the aggregated level. This may explain why the impact of obesity is still confounded and appears to be positive in Model 4. In Model 5, an interaction of smoking and obesity is added. Both smoking and obesity are now found to be associated with higher mortality and interact with each other negatively. This is consistent with findings in the literature (Koster et al., 2008; Krueger, Rogers, Hummer, & Boardman, 2004). Although the effects of smoking and obesity are not directly comparable using the coefficient estimates because of their different metrics, it is possible to compare the individual impact of smoking and obesity on men relative to women. For mortality, the coefficient of the smoking covariate for men is almost twice of that for women, the coefficient of obesity for men is nearly 6 times of that for women, and the coefficient of interaction for men is 4 times of that for women. This suggests men are more responsive to the impact of smoking and obesity on mortality even when interaction is taken into account, confirming the gender-difference arguments in existing studies (Chao et al., 2002; E. A. Finkelstein, Brown, Wrage, Allaire, & Hoerger, 2010).

In contrast, despite the small magnitude, smoking alone is shown to increase the net disability transition rate for men but decrease it for women, while the signs are reversed for the effects of obesity in Model 3 just as in the models for mortality. This is likely because for men the past decline in smoking has averted more disability incidence than the rise in obesity prevalence has caused, but for women it is the opposite as a result of both the delayed trend of smoking and obesity's greater disabling impact for women (Reynolds & McIlvane, 2009; Reynolds et al., 2005; Whitson et al., 2010). Including both covariates only partially removes the bias, while adding the interaction term produces results suggesting that both smoking and obesity are associated with higher risks of becoming disabled. Furthermore, compared to the estimates from Model 5 for female mortality, the estimates from Model 5 for female disability yield a larger effect for obesity but a disproportionately smaller effect for smoking, while the effects for interaction are similar, suggesting that obesity contributes to a greater proportion of female disability than to female mortality. For men, in contrast, the relative impacts of smoking and obesity are roughly the same for both mortality and disability.

Overall, the addition of both smoking and obesity covariates and their interaction explains respectively 25% and 10% of the variances of mortality and disability that are otherwise left unexplained by simple Lee-Carter model with no covariates. Specifically, the adjusted R-squares increase from 0.9461 to 0.9597 for mortality and from 0.9884 to 0.9895 for disability. Accordingly, projections of the transition rates are made based on the relationship discovered in Model 5 for both mortality and disability.

Figure 2.4A and Figure 2.4B present the estimates for $a(x)$, $b(x)$ and $k(t)$ from Model 1 and Model 5 respectively. Again, due to the assumption of a constant impact of disability on mortality, the estimates of $k(t)$ and $b(x)$ are identical for mortality for disabled and non-disabled, although the estimates for $a(x)$ for these two types of transition differ. The addition of covariates and interaction does not lead to substantial change in $k(t)$. In fact, as shown in Figure 2.5, the estimates of $k(t)$ for both mortality and disability for models with and without covariates are very close. Nevertheless, when $k(t)$ is multiplied by $b(x)$ and then added to $a(x)$ which both change substantially due to different model specifications, variations in transition rates and their translations into life expectancy can still be striking. The comparison of the plots of $a(x)$ for mortality demonstrates that the inclusion of the two covariates and their interaction explains a great proportion of the gender-difference in the underlying mortality profile by age. Furthermore, in Figure 2.4A the underlying disability incidence rates at younger ages are higher for men than women, reflecting the greater reduction in cumulative smoking history for men at younger ages, which results in a higher survival of the already disabled or potentially disabled population. This bias disappears once covariates and interaction are included, and the underlying disability incidence appears to be higher for women particularly at higher ages, consistent with previous epidemiologic studies that find women are more vulnerable to disabling conditions such as fractures, osteoarthritis and back problems (Reynolds & McIlvane, 2009; Reynolds et al., 2005; Whitson et al., 2010).

Similar to the findings in Wang and Preston (2009), when smoking and obesity are not adjusted for in the Lee-Carter models, the disparities in the $b(x)$ estimates

between men and women are evident for both mortality and disability. Once smoking and obesity are included, the disparities become much smaller and the slopes of the age pattern of change in transition rates become more level, as shown in Figure 2.4B. Specifically, the $b(x)$ estimates for mortality for men and women show less distorted pattern. Similarly, those estimates for disability for men and women are more parallel and their differences are reduced by approximately 40%. Moreover, for younger ages, the age-specific mortality change in response to the temporal trend of mortality change is larger than for older ages in Figure 2.4A, but smaller in Figure 2.4B. Since the younger cohorts have experienced more remarkable declines in smoking but increases in obesity, the above result indicates that adjusting for the time trends of smoking and obesity produces a less distorted age pattern of mortality change. Also, the impacts of smoking decline are more salient than the impacts of obesity increase.

Figure 2.6 compares the ratio of projected transition rates at 2040 to those observed at 2010 for Model 1 and Model 5. Because the impact of disability on mortality is assumed to be constant over age, the ratios for mortality of disabled and of non-disabled are identical. Therefore, only the graph for the ratio for mortality of non-disabled is shown. On the one hand, the ratios of mortality (both disabled and non-disabled) estimated using both model specifications for women are greater than the ratios for men, reflecting men's sharper decline in smoking among these cohorts. Inclusion of covariates leads to lower mortality as expected. For both sexes, the differences in ratios for disabled/ non-disabled mortality estimated with and without covariates are greater at older ages, as the cohorts that will reach older ages by the end of the projection period are the ones experienced the largest smoking decline. Contrarily, inclusion of covariates

leads to higher disability incidence. And the differences in ratios for disability estimated with and without covariates are greater at younger ages, reflecting the fact that the obesity epidemic is more recent. This may also suggest that in the future disability is more likely to be attributable to obesity than to smoking.

Furthermore, model selection has a greater impact on disabled/ non-disabled mortality projection for women but a greater impact on disability projection for men. Given men and women have similar patterns in cohort obesity history as shown in Figure 2.2, the difference in projections due to different model selection seems to originate from the gender difference in smoking history. The larger impact of model selection on mortality projection for women, particularly at older ages, is consistent with the timing of extinction of the heaviest smoking female cohorts. Similarly, the disability projection for men is more sensitive to model selection, particularly at younger ages, because men's extended trend of smoking decline has provided relatively larger exposure for the disabling effect of obesity to operate.

Figure 2.7 presents the projected mortality and disability transition rates over time relative to the observed ones in 2010, for several age groups. Overall, all age groups for both sexes will experience decline in mortality and disability incidence. The oldest cohort in this figure is born in 1925-1929, which is younger than the heaviest smoking male cohort but older than the heaviest smoking female cohort. Therefore, the mortality associated with smoking will decline steadily for men across all cohorts. However, the younger cohorts, particularly for those born after 1955 (aged 55 in 2010), have substantially higher prevalence of obesity that offsets the smoking-related mortality

declines. Thus, a crossover is seen on the graph for male mortality. The decline in smoking for women, on the other hand, only occurred for cohorts born after 1945. Therefore, the pattern of mortality decline for women across cohorts is more complex, given both directions of change in smoking-related mortality and the increase of obesity prevalence as well as their interaction. Nevertheless, in general, the obesity epidemic seems to reduce the rates of mortality decline for women as well.

Besides mortality, the incidence of male disability is also expected to decline for all age groups over time. Compared to the projected trends of male mortality and female disability, male disability shows less of a cohort pattern, except for cohorts born recently that have highest prevalence of obesity. This indicates that smoking is more likely to have a fatal than disabling effect for men, while obesity is disabling for men but the effect is not as strong as it for women. The decline in male disability incidence is more likely to be attributable to improvement in medical care that affects the underlying mortality profile at all ages. For women, a clear cohort pattern can be seen for all age groups. Additionally, this pattern is only observed among cohorts born after 1950, suggesting that this cohort pattern originates from the increase in obesity prevalence rather than from the change in smoking. Therefore, it is consistent with previous studies that argue obesity has stronger impact on female disability.

Finally, the life expectancy (LE), disability-free life expectancy (LE^{ND}) and life expectancy with disability (LE^D) between age 55 and 85 are projected up to 2040 for both sexes, as shown in Table 2.2 and Figure 2.8. In accordance with the findings in Crimmins et al. (1997, 2009), I find the US elderly have experienced substantial increases in both

LE and LE^{ND} during the observation period from 1980s to 2010, and the increases in LE is mostly attributable to the increase in LE^{ND} along with the decrease in LE^D , suggesting compression of disability (Crimmins, Hayward, Hagedorn, Saito, & Brouard, 2009; Crimmins, Saito, & Ingegneri, 1997). While this is true for both sexes, men appear to benefit from more years of gain in LE^{ND} than women.

Standard Lee-Carter model projects continued gains in LE and LE^{ND} for men and women in the coming decades, although with slower rates of increase than the previous 30 years. Compared to 2010, men will have 1.72 years gain in LE between age 55 and 85, whereas the figure for women is half of it. The gains in LE can be decomposed to about 1-year loss in LE^D for both sexes, and about 2.7 years and 1.7 years gain in LE^{ND} for men and women respectively.

For men, the addition of cohort smoking and obesity history, along with their interaction, yields even more optimistic projections than the model with no covariates. Relative to Model 1, Model 5 projects an extra 0.30, 0.57 and 0.70 years gain in LE at 2020, 2030 and 2040 respectively, and an extra 0.22, 0.41 and 0.50 years gain in LE^{ND} at 2020, 2030 and 2040 respectively. This indicates that net of the increase in obesity prevalence, the decline in smoking still leads to progressive gain in the adjustments of life expectancy for American men over the next three decades, of which over 70% is attributable to increase in disability-free life expectancy.

In contrast, including both covariates and their interaction produces a smaller increase of LE and LE^{ND} for women, because of the slower improvement in survival produced by their lagged decline in smoking during the observation period. Compared to

Model 1, this model only leaves women an additional 0.19, 0.24 and 0.19 year of LE at 2020, 2030, and 2040 respectively, and an additional 0.09, 0.05 and 0.03 year of LEND at 2020, 2030, and 2040 respectively. As the heaviest smoking female cohort reaches its prime age of death in 2020s, the decline in gains in LE and LEND adjustments over time relative to the model without covariates can be best explained by the fact that obesity has large destructive impact on women's health.

Moreover, both sexes are expected to spend a larger proportion of their remaining life time disability free. Relative to the model without covariates, however, the model proposed in this study produces only slightly smaller of this proportion for men throughout the projection period but an almost 1% decrease for women by 2040. This indicates the impact of fall in smoking and the impact of rise in obesity prevalence tend to balance each other out for men in terms of quality of health, but for women the negative effect of rise in obesity will likely to outweigh the positive effect of fall in smoking in the next 25 years, confirming the findings in existing literature about the gender difference in the impacts on mortality and morbidity of both smoking and obesity.

Model Validation

In addition to measuring the goodness-of-fit for the forecasting model using R-squares, I perform out-of-sample model validation by holding out the data from 2001 to 2010 and comparing these data with 10-year projections made with data only from 1982-2000. For men, the maximum error relative to the observed value is roughly 0.22 year for

LE, 0.35 year for LE^{ND} and 0.29 year for LE^D . For women, it is 0.16 year for LE, 0.19 year for LE^{ND} and 0.23 year for LE^D . In conclusion, these results indicate the forecasting model is valid and generalizable for data from varying periods.

Sensitivity Analyses

The NHIS data used in this study is limited to the non-institutionalized population which is presumably healthier than the institutionalized population. Therefore, the net disability transition rate tends to be underestimated. I evaluate the magnitude of this underestimation by performing the analysis with additional data from the American Community Survey (ACS) for the institutionalized population. In addition to variables indicate whether a respondent has limitations in activity, a variable that indicates whether one resides in institutions is available from 2006 to 2010. I calculate the prevalence of disability for the entire population using these information and re-run the forecasting model. Relative to the life expectancy measures for 2006-2010 calculated in this practice, using data for only non-institutionalized population overestimates the LE by a maximum of 0.002 year and the LE^{ND} by a maximum of 0.15 year, but underestimates the LE^D by a maximum of 0.15 years for men. For women, the LE and the LE^{ND} are overestimated by a maximum of 0.003 year and 0.26 year, and the LE^D is underestimated by a maximum of 0.26 year. Moreover, I use the estimates from this analysis and project the LE^{ND} and LE^D for 2011-2015 and compare these projections with those from projections based on NHIS surveys in 2006-2010. If only data for the non-institutionalized population is used, the projections for the LE and the LE^{ND} in 2011-2015 are overestimated by a maximum of

0.03 year and 0.14 year respectively, but the projection for the LE^D is underestimated by a maximum of 0.12 year. For women, the LE and the LE^{ND} are overestimated by a maximum of 0.003 year and 0.18 year respectively, but the projection for the LE^D is underestimated by a maximum of 0.18 year. Therefore, the effect of excluding the institutionalized population on the estimates and projections can be considered small.

Furthermore, the proposed model is subject to two assumptions: 1) the impact of disability on mortality is constant over age. 2) There is no recovery from being disabled. Two additional sensitivity analyses are performed to test the robustness of the model, by estimating the effects of violation of these two assumptions on age-specific transition rates and its aggregated effects on healthy life expectancy at age 55.

As suggested in Guillot and Yu 2009, I model both the relative mortality risk of disability and the probability of recovery as exponential functions of age as below

$$HR_x = \alpha_1 e^{\beta_1 x}$$

$$q_x^{UH} = \alpha_2 e^{\beta_2 x}$$

The parameter estimates from Guillot and Yu 2009 is used for the values of α_1 (5.51), β_1 (-0.049), α_2 (0.353) and β_2 (-0.043). These parameters are estimated for men and women combined based on data from Health and Retirement Study (HRS) 1998 and 2000 with a transformed age $a=x-65$. Results of projected healthy life expectancy at 2010, 2020, 2030 and 2040 are shown in Table 2.3A and Table 2.3B.

When it is modeled as an exponential function, the mortality risk of being disabled can be as high as 8.98 times and as low as 2.06 times of the mortality risk of

being healthy at age 55 and 85 respectively. Once translated into healthy life expectancy, however, the effect of violation of the constant impact of disability on mortality assumption produces only small changes, as shown on Table 2.3A. Overall, increase in the relative mortality risk of disability leads to only 0.15 year increase in LE^{ND} , 0.13 year decline in LE^D and hence 0.02 year increase in LE for males by the end of the projection period. Similarly, the corresponding changes for females are 0.18 year increase in LE^{ND} , 0.2 year decrease in LE^D and 0.02 year decreases in LE at 2040.

Neither does the inclusion of recovery from being disable result in substantial changes in the projection of future healthy life expectancy. Table 2.3B shows that including recovery in the model yields gain in LE^{ND} and loss in LE^D for both sexes. The maximum gain in LE^{ND} is 0.14 year for both men and women, while the maximum loss in LE^D is 0.13 year and 0.08 year for men and women respectively. Overall, the gain in LE^{ND} and loss in LE^D offset each other, and hence lead to respectively 0.1 year and 0.08 year gain in LE for men and women.

Conclusion

Smoking and obesity both have independent negative influences on individuals' health, including both survival and activities. Operating jointly, they unanimously raise mortality for both disabled and non-disabled. However, their interplay may yield different possibilities for disability, as both the incidence and prevalence of disability have to do with survival which is affected by the two risk factors in a different direction. To some extent, this results in a competition between death and disability.

This study uses summary measures (LE^{ND} and LE^D) to evaluate the quality of health for the US adults aged 55 years old and above in the past and future, in association with observed and projected trends of smoking and obesity. Estimates from the modified Lee-Carter model suggest that a large proportion of the difference in mortality and disability between men and women can be attributed to their different smoking patterns and the gender difference in the impacts of smoking and obesity.

Men and women are both expected to have rising LE and LE^{ND} as well as falling LE^D over the next 25 years, resulting in compression of disability. However, mostly due to gender difference in smoking history, men will benefit more from their earlier decline in smoking and have larger improvement in LE than women, narrowing the gender gap in current LE down to 0.5 year by 2040. In addition to extending life expectancy, the combined effects of existing and expected change in smoking and obesity will likely lead to more years living without disability and fewer years living with disability. Specifically, men are projected to have a 3.2 years increase in LE^{ND} over the 30-year forecasting period, almost twice the gain for women. Besides men's advantage in LE due to an earlier start in smoking decline, this difference in LE^{ND} may as well be partially attributable to the greater impact of obesity on disability for women, which offsets some of the gains in LE^{ND} produced by the smoking decline.

Figure 2.1: Disability Prevalence for US Elderly (1982-2010)

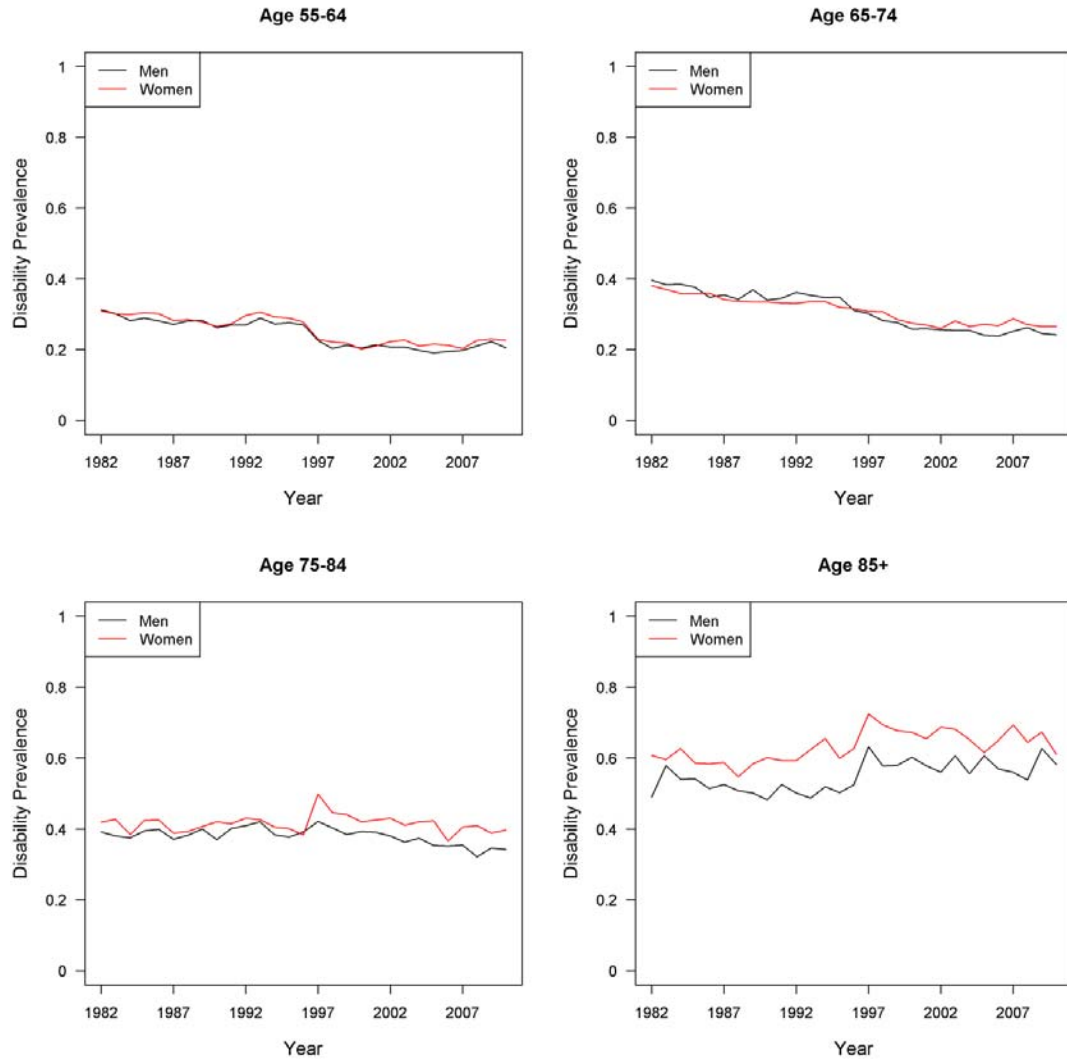


Figure 2.2: Smoking and Obesity Trends by Birth Cohorts

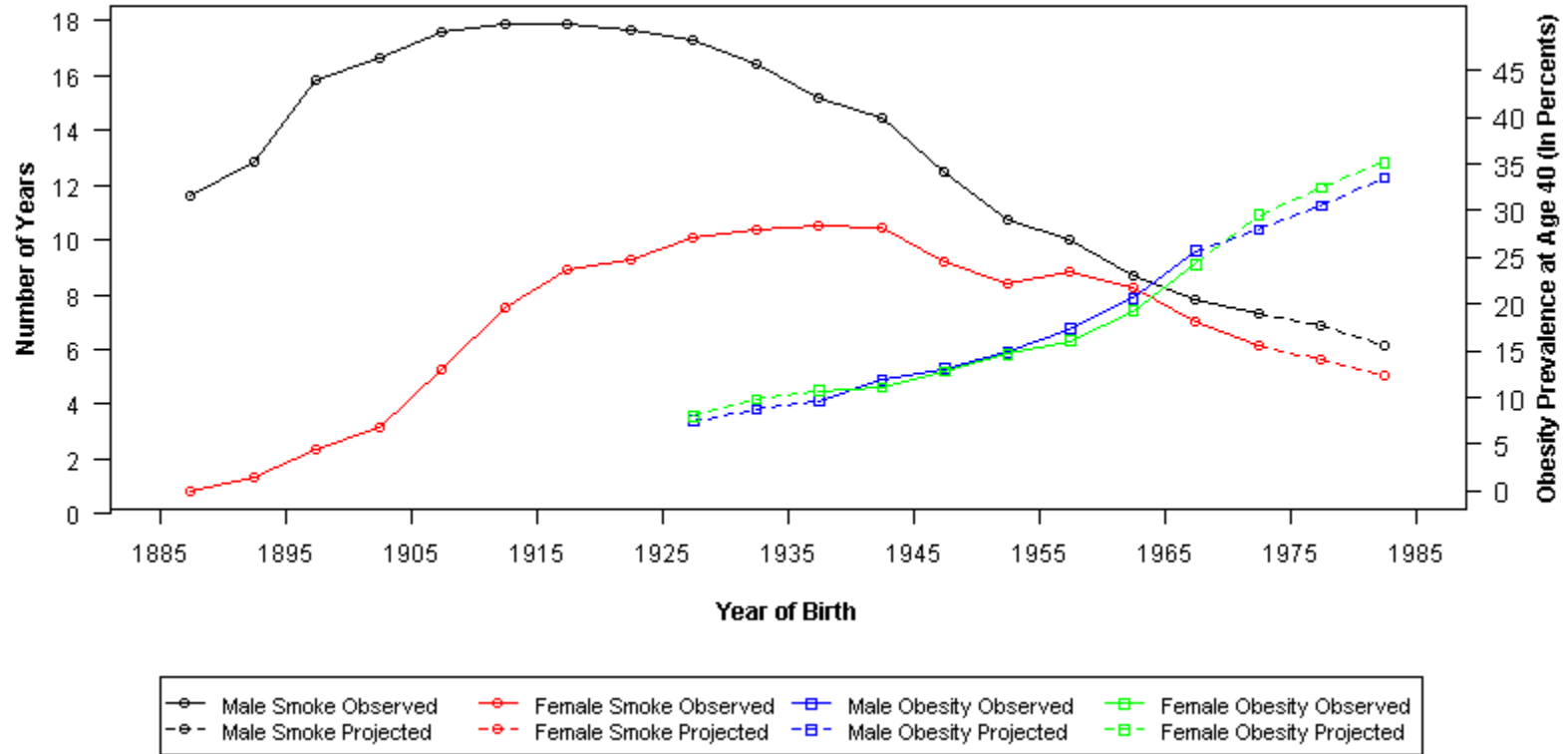


Figure 2.3: Normalized Transition Rates over Time (1982-2010)

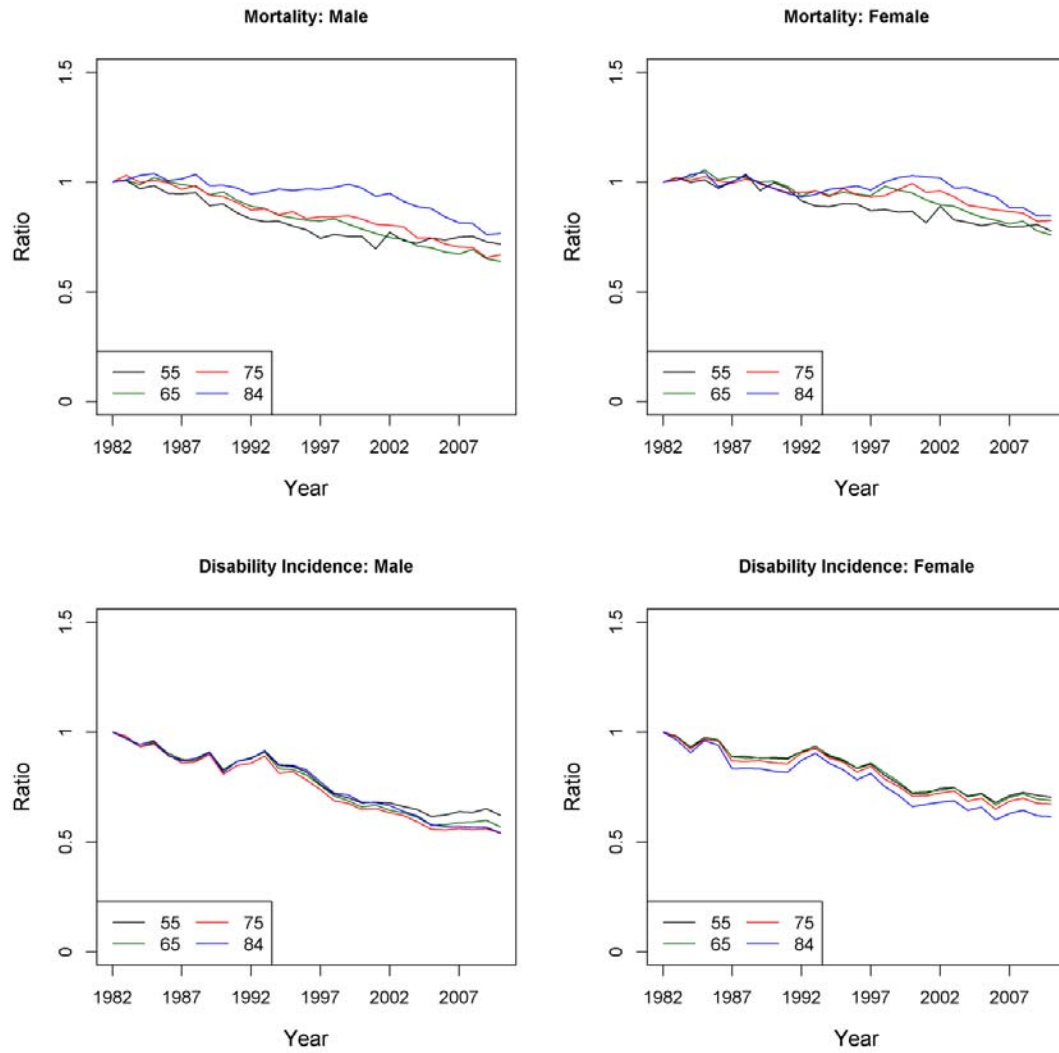
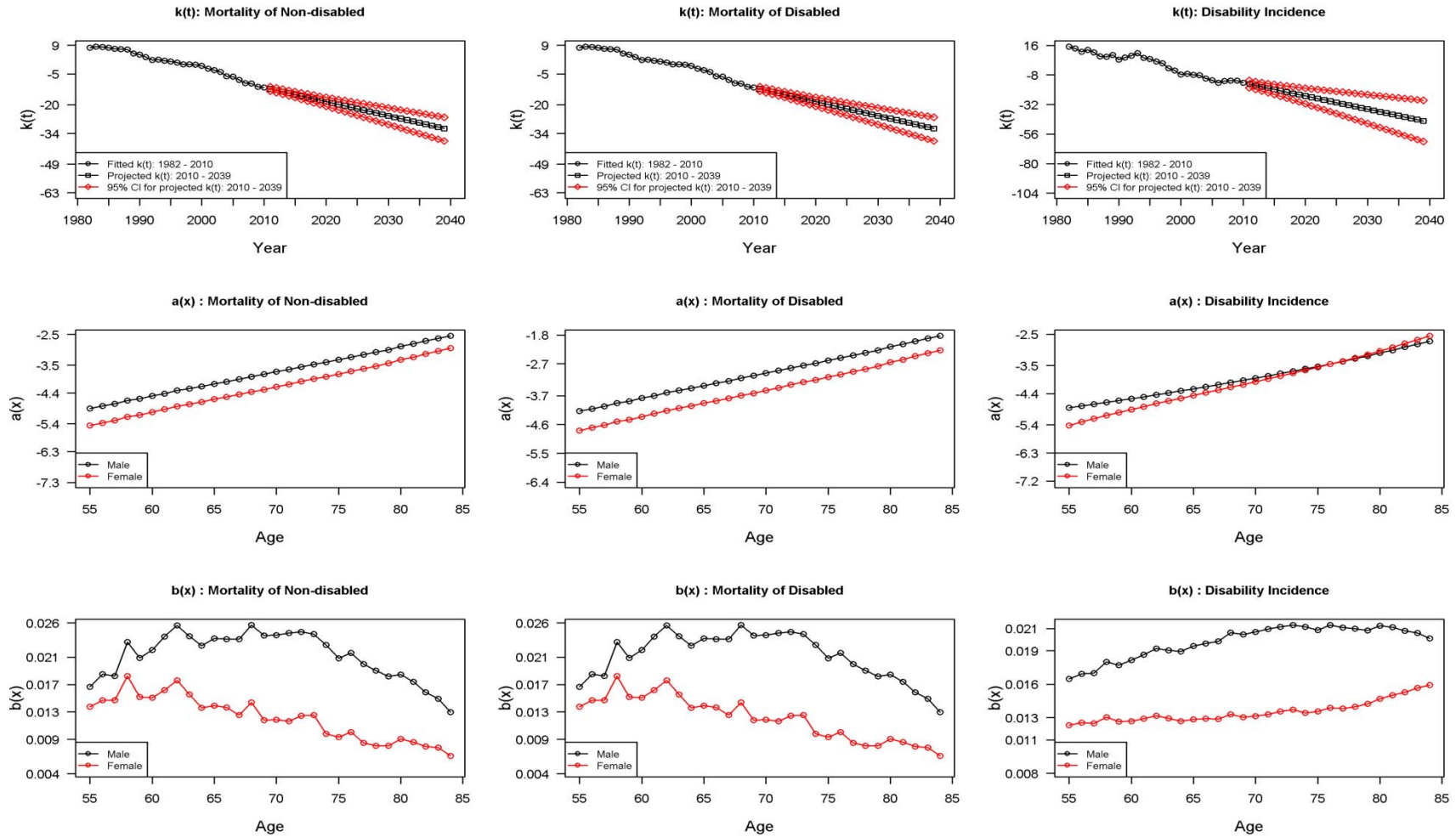


Figure 2.4: Parameter Estimates of the Lee-Carter Model

A. Without Covariates



B. With Smoking, Obesity and Interaction

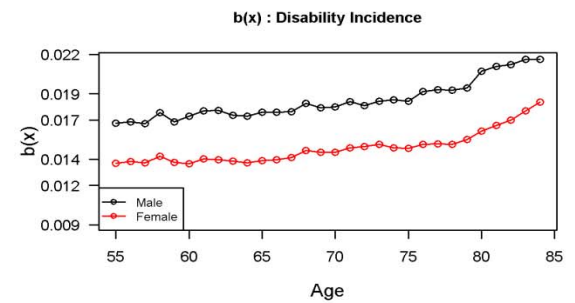
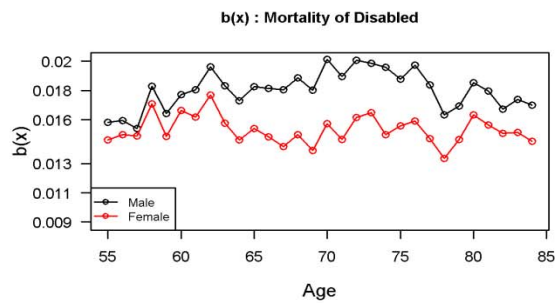
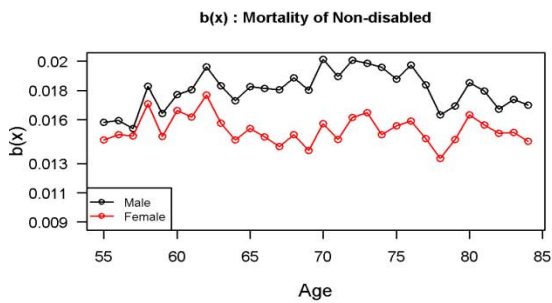
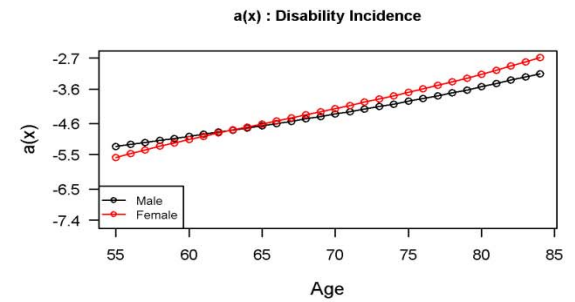
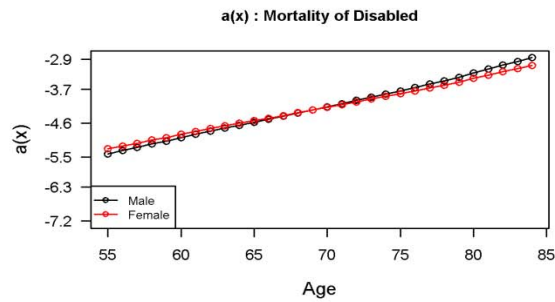
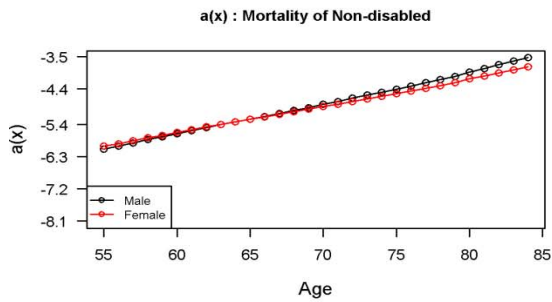
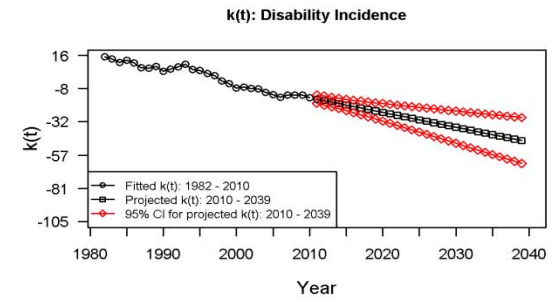
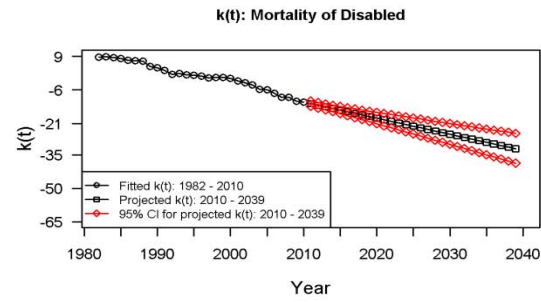
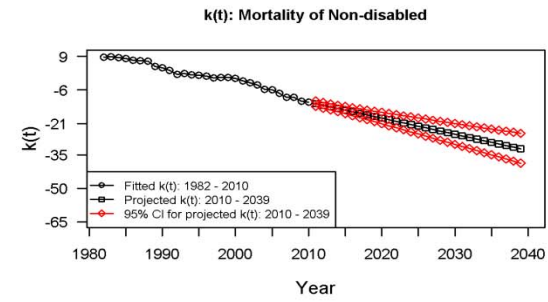


Figure 2.5: Comparison of kt values in models with and without covariates

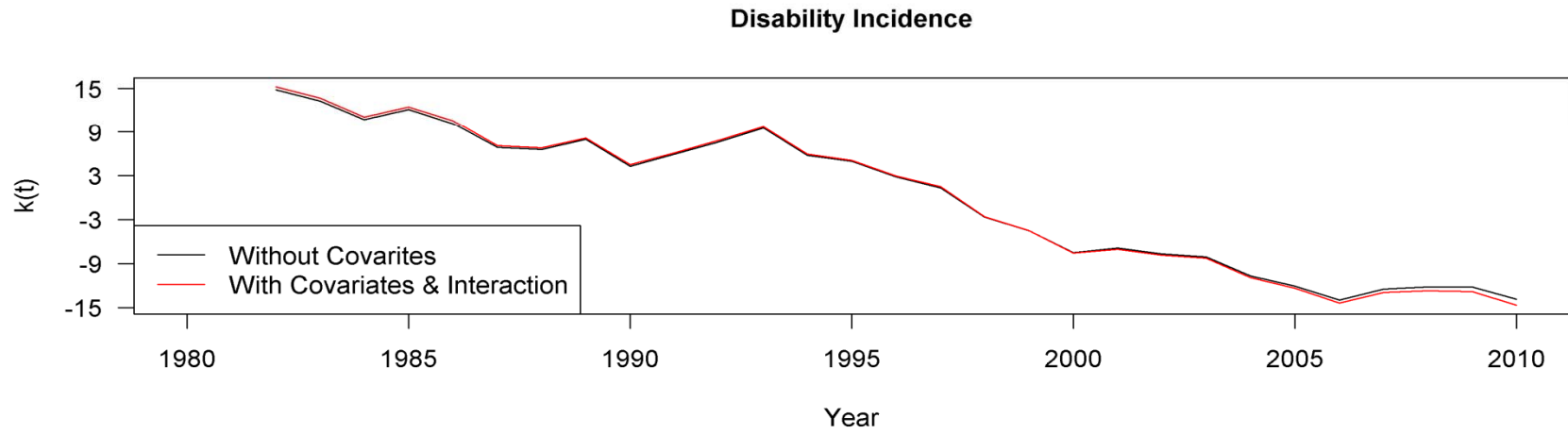
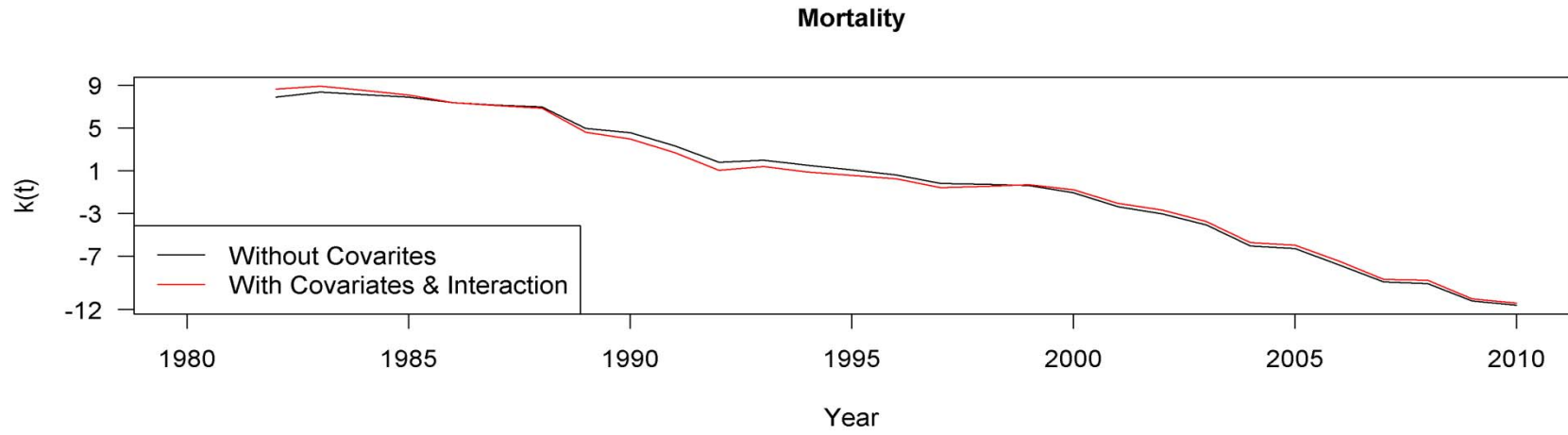


Figure 2.6: Ratios of Projected Transition Rates in 2040 to Transition Rates Observed in 2010

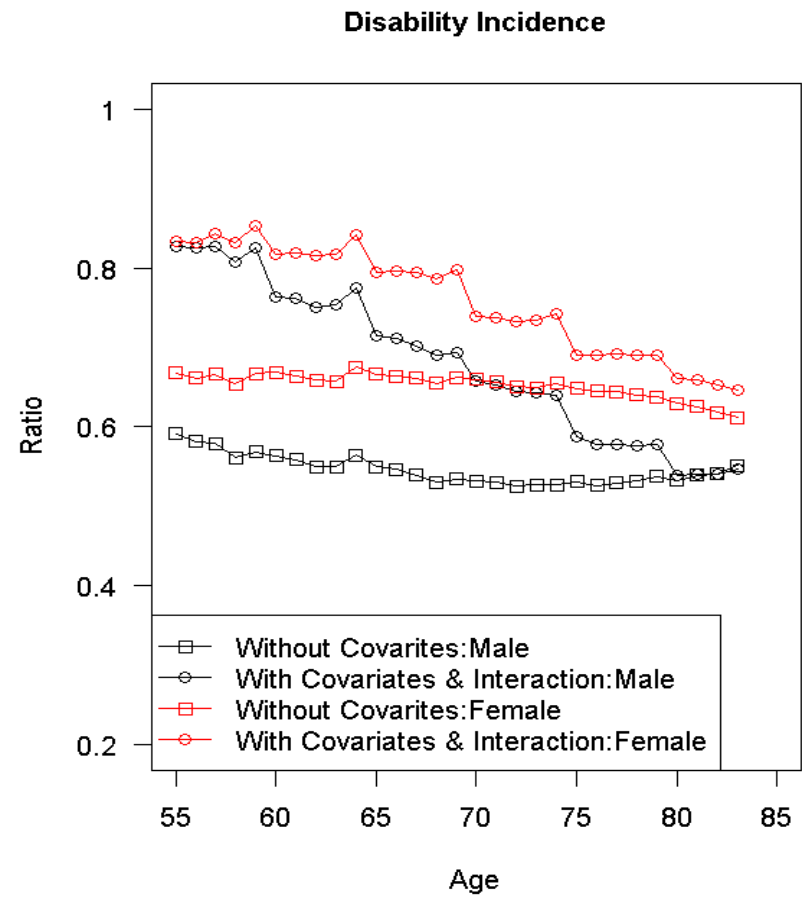
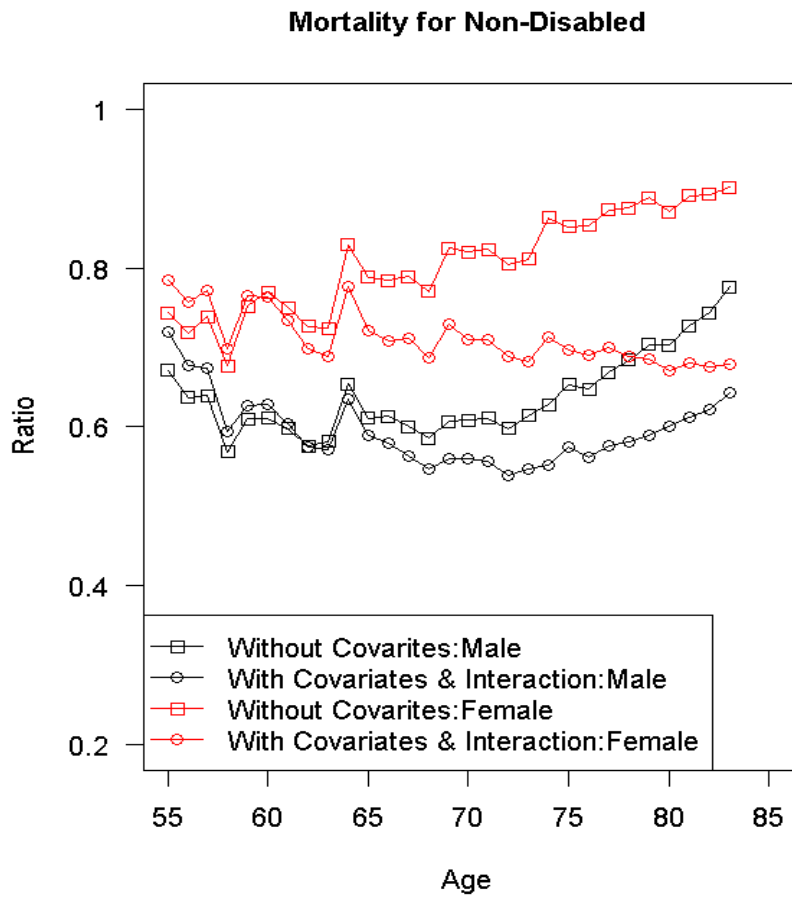


Figure 2.7: Normalized Transition Rates over Time for the Forecasting Period (2010-2040)

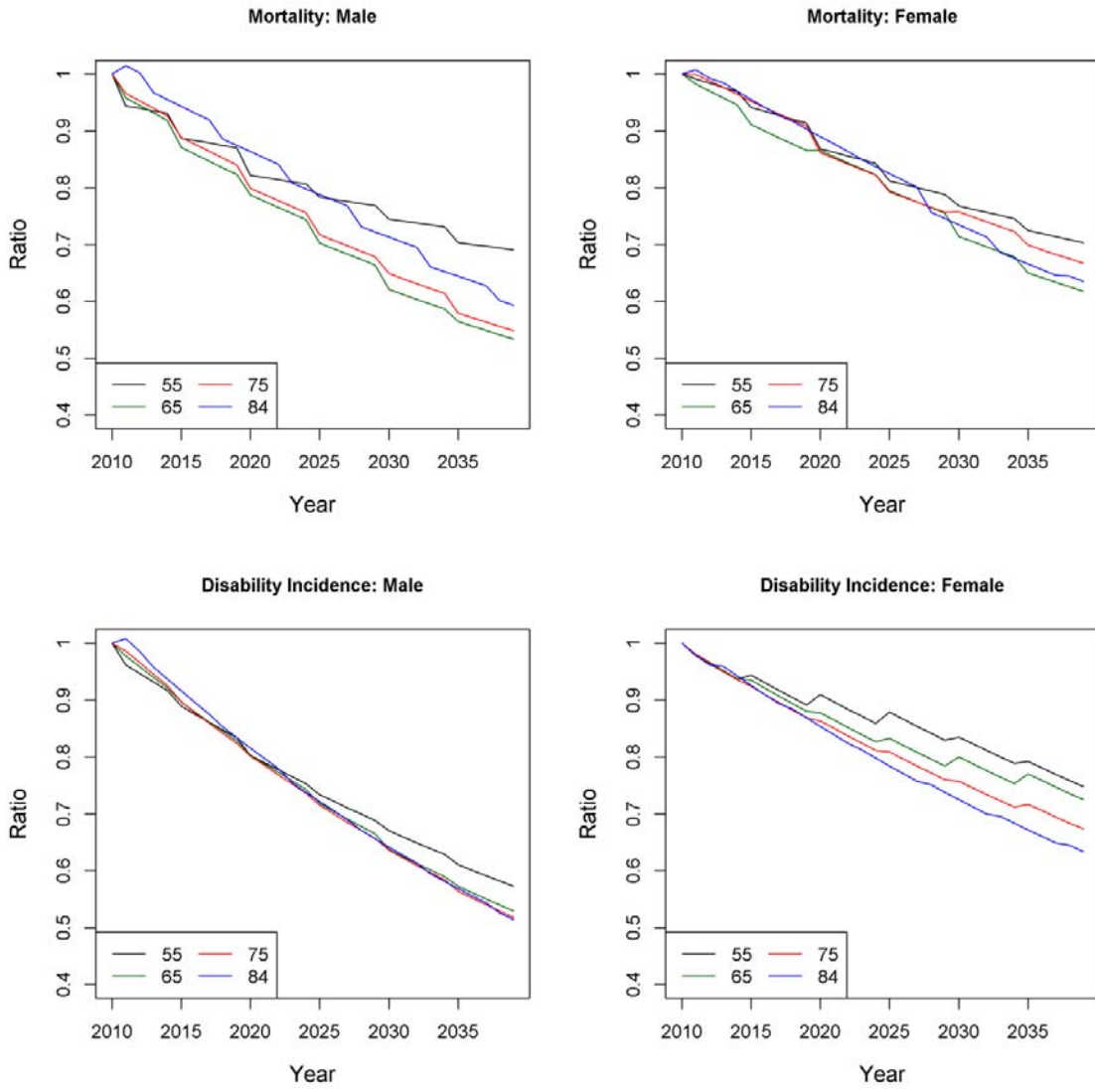


Figure 2.8: Observed and Projected Healthy Life Expectancy (LE and LEND) Using Different Models

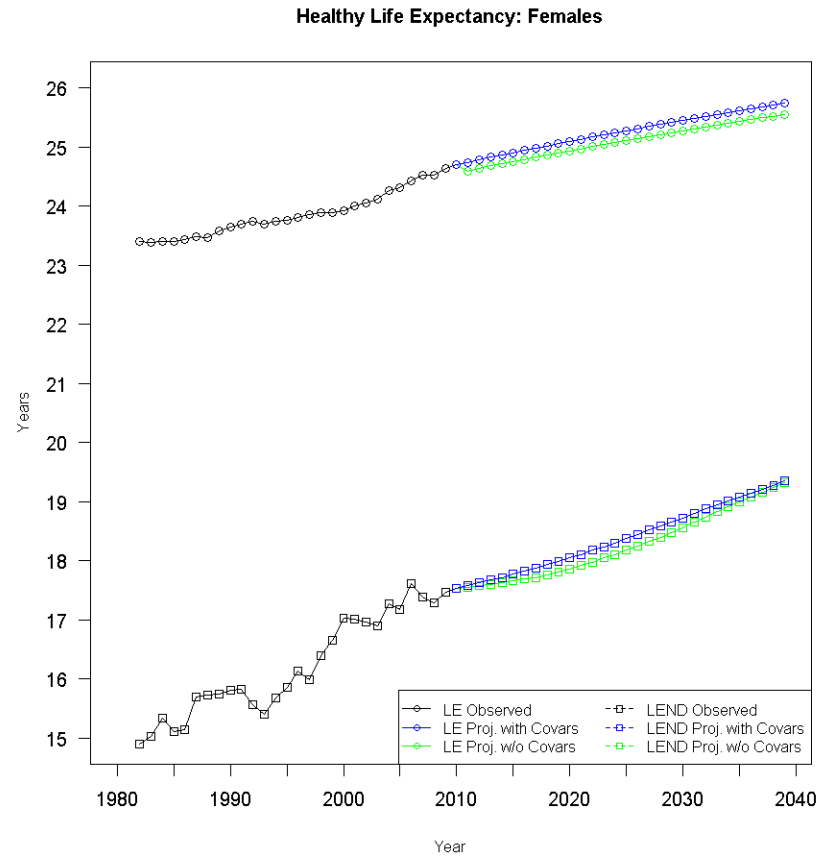
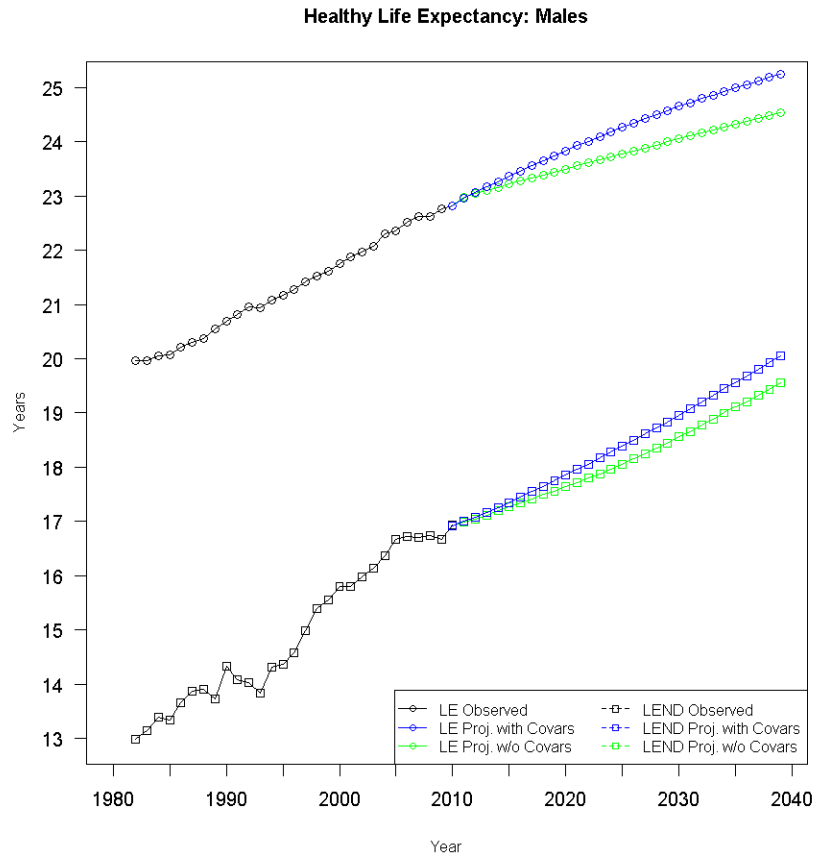


Table 2.1: Parameter Estimates from Different Models

		Mortality					Net Disability Incidence				
		Model 1	Model 2	Model 3	Model 4	Model 5	Model 1	Model 2	Model 3	Model 4	Model 5
Male	Smoking	-	0.0266	-	0.0263	0.0668	-	0.0078	-	0.0036	0.0255
	Obesity	-	-	-0.0129	-0.0077	0.0674	-	-	-0.005	-0.0035	0.0289
	Interaction	-	-	-	-	-0.0042	-	-	-	-	-0.0018
Female	Smoking	-	0.0222	-	0.0161	0.033	-	-0.0002	-	0.0006	0.0088
	Obesity	-	-	-0.0038	-0.0012	0.0115	-	-	0.0069	0.0068	0.0181
	Interaction	-	-	-	-	-0.001	-	-	-	-	-0.0011
R-Square		0.9461	0.9528	0.9311	0.9494	0.9597	0.9884	0.9881	0.9889	0.9888	0.9895

Table 2.2: Life Expectancy between Age 55-85 by Disable Status

	Males					Females			
	Year	LE	LE ND	LE ^D	LE ND /LE (%)	LE	LE ND	LE ^D	LE ND /LE (%)
Observed	1982	19.96	12.98	6.98	65.03	23.40	14.90	8.50	63.68
	1990	20.70	14.32	6.38	69.18	23.64	15.82	7.82	66.92
	2000	21.75	15.80	5.95	72.64	23.92	17.04	6.88	71.24
	2010	22.82	16.92	5.90	74.15	24.69	17.53	7.16	71.00
Projected without Covariates	2020	23.53 (23.26, 23.77)	17.64 (17.45, 17.83)	5.89 (5.73, 6.02)	75.00 (74.57, 75.49)	24.92 (24.81, 25.03)	17.91 (17.81, 18.00)	7.01 (6.91, 7.10)	71.89 (71.56, 72.18)
	2030	24.06 (23.60, 24.43)	18.58 (18.21, 18.95)	5.48 (5.10, 5.80)	77.22 (76.14, 78.59)	25.25 (25.08, 25.43)	18.62 (18.37, 18.83)	6.64 (6.42, 6.90)	73.72 (72.79, 74.49)
	2040	24.54 (23.94, 25.01)	19.6 (19.04, 20.13)	4.94 (4.40, 5.45)	79.87 (78.11, 81.86)	25.55 (25.33, 25.77)	19.27 (18.96, 19.68)	6.18 (5.86, 6.59)	75.82 (74.36, 76.98)
Projected With Covariates and Interaction	2020	23.83 (23.58, 24.05)	17.86 (17.70, 18.03)	5.97 (5.81, 6.14)	74.95 (74.41, 75.45)	25.11 (24.95, 25.24)	18.00 (17.89, 18.13)	7.09 (6.99, 7.21)	71.72 (71.32, 72.08)
	2030	24.63 (24.24, 24.98)	18.99 (18.68, 19.36)	5.62 (5.30, 6.06)	77.17 (75.61, 78.38)	25.49 (25.23, 25.69)	18.67 (18.41, 18.97)	6.80 (6.54, 7.13)	73.28 (72.13, 74.23)
	2040	25.24 (24.75, 25.67)	20.10 (19.60, 20.64)	5.10 (4.65, 5.78)	79.79 (77.35, 81.53)	25.74 (25.40, 26.00)	19.30 (18.88, 19.77)	6.41 (6.00, 6.96)	75.03 (73.07, 76.53)

Table 2.3: Sensitivity of Results to Alternative Assumptions

A. Non-constant Impact of Disability on Mortality

	Males			Females		
	LE	LE ND	LE ^D	LE	LE ND	LE ^D
2010	-0.02	0.01	-0.03	0.02	0.02	0
2020	-0.01	0.07	-0.06	-0.01	0.01	-0.03
2030	0	0.12	-0.12	-0.03	0.1	-0.13
2040	0.02	0.15	-0.13	-0.02	0.18	-0.2

A positive value means that the alternative assumption resulted in a gain in life expectancy relative to the main model

B. With Recovery

	Males			Females		
	LE	LE ND	LE ^D	LE	LE ND	LE ^D
2010	0.05	0.11	-0.06	0.04	0.12	-0.08
2020	0.03	0.12	-0.09	0.02	0.1	-0.08
2030	0.1	0.14	-0.04	0.08	0.1	-0.02
2040	0.07	0.2	-0.13	0.08	0.14	-0.06

A positive value means that the alternative assumption resulted in a gain in life expectancy relative to the main model

Chapter 3 Estimating the Effects of Obesity and Weight Change on Mortality Using a Dynamic Causal Model

Introduction

Many studies investigate the association between obesity and mortality (Adams et al., 2006; Allison, Faith, Heo, & Kotler, 1997; Berrington de Gonzalez et al., 2010; Comoni-Huntley, Harris, & Everett, 1991; Katherine M Flegal, Kit, Orpana, & Graubard, 2013; Gelber, Kurth, Manson, Buring, & Gaziano, 2007; Manson, Stampfer, Hennekens, & Willett, 1987; Singh & Lindsted, 1998; Tayback, Kumanyika, & Chee, 1990).

Although it is commonly agreed that low body weight and severe obesity are associated with increased mortality risks, whether overweight and moderate obesity is protective or hazardous are still in debate (Adams et al., 2006; Katherine M Flegal et al., 2013; Lantz, Golberstein, House, & Morenoff, 2010; N. Mehta & Chang, 2009). A well-known challenge in estimating the mortality risks of obesity is reverse causality attributable to illness-associated weight loss. Reverse causality is thought to downwardly bias the observed mortality risks of obesity, because low weight and weight loss are often a result of illness or smoking that is associated with increased mortality. 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 associated with disease-induced weight loss and estimates among smokers are also

thought to be highly influenced by reverse causal processes. These diseases include chronic obstructive pulmonary disease (COPD), many cancers, cardiac diseases, and renal disease (Claessen, Brenner, Drath, & Arndt, 2012; He, McGee, Niu, & Choi, 2009; He, 2011; S. H. Preston, Mehta, & Stokes, 2013; Reas, Nygård, Svensson, Sørensen, & Sandanger, 2007).

To date, most attempts to deal with reverse causality are thought to be inadequate (N. K. Mehta & Chang., 2011). The most common practices to account for reverse causality in longitudinal studies are excluding subjects with preexisting diseases at baseline (Allison, Fontaine, Manson, Stevens, & VanItallie, 1999; Singh & Wang, 2001; Stewart et al., 2009), excluding subjects that experienced substantial weight loss (≥ 10 lb) in previous years (Allison, Faith, Heo, Townsend-Butterworth, & Williamson, 1999; Evans & Frank, 1997), and excluding the first few years of follow-up in order to eliminate premature deaths that were potentially caused by illness present at baseline (Allison, Faith, et al., 1999; Katherine M Flegal, Graubard, Williamson, & Cooper, 2011; Singh & Wang, 2001). These strategies often lead to waste of substantial amount of data, and deletion of large proportion of deaths, reducing statistical power and potentially causing more biases than eliminating them (Ajani et al., 2004; Baik & Ascherio, 2000; Evans & Frank, 1997).

Among those with relatively better data for information in body weight history and diagnosis history of diseases, only a few studies (Claessen et al., 2012; He et al., 2009; He, 2011; S. H. Preston et al., 2013) attempt to examine the association between weight status and mortality risks from a dynamic perspective. Most studies only use a

single measurement for weight status, confounders, and other relevant covariates measured at baseline. Some studies show that instead of using a stock measure of weight status taken at one point in time, a flow measure such as change in body weight is a stronger predictor of mortality risks, especially for the elderly (Mikkelsen, Heitmann, Keiding, & Sørensen, 1999; Myrskylä & Chang, 2009; Somes, 2002).

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. Thus, diseases operate as both confounders and mediators along the causal pathway, making conventional analytical methods produce biased estimates (Hernán & Robins, 2006; J M Robins, Hernan, & Brumback, 2000). Diagram A1 in the Appendix shows a simple example with only two time points. Weight change occurred at $t(0)$ has impact on the incidence of chronic diseases between time $t(0)$ and time $t(1)$, which in turn affects weight change at $t(1)$ and raises the probability of death. In the mean time, the final outcome, death, may be affected by weight change at both time points. A more complex example with comprehensive causal pathway can be seen in Diagram A2 in the Appendix.

The present study attempts to address the time-varying confounding of the body weight and mortality association by applying a marginal structural model (MSM) (Hernán & Robins, 2006; J M Robins et al., 2000; James M Robins, 1998) to a nationally representative sample. I specifically fill the gaps in existing literature by: (1) modeling both baseline weight and time-varying weight change using multiple waves of interviews,

and (2) treating both incident illness and health behaviors as time-varying confounders. To my knowledge, no prior study has used a marginal structural model to estimate the mortality risks of obesity and body weight change.

Data

Sample

Data for this study are extracted from a nationally representative dataset, the Health and Retirement Study (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 (HRS 2010). Analyses in this study are performed with the RAND HRS data, version L (RAND, 2011). As a prospective study, HRS serves the purpose of this study better than retrospective studies that are used in many prior studies. Each respondent's current body weight, health conditions, health behaviors, as well as other relevant characteristics are asked at each HRS interview. In contrast, retrospective studies rely on respondents' recalling their personal history, thus making it less possible to collect data that is as accurate and contains as many repeated measures for relevant variables as the HRS does. Additionally, retrospective studies are more likely to have selection bias problem. For instance, the individuals who were severely obese may not have survived to the survey to report their weight history.

In this paper, I only include the initial HRS cohort that 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. These two cohorts entered the survey at approximately same age (50-60 years old) and are both interviewed every two years.

The initial HRS cohort and the WB cohort have a sample size of 9,763 and 2,760 respectively, making a total of 12,523 respondents. In order to calculate weight change between subsequent interviews, I 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. I further exclude outliers that with very high baseline BMI (>60) and that have experienced extraordinary weight loss ($>30\%$ of body weight) between two consecutive interviews. This leads to a sample of 8,678 respondents and 67,772 observations (person-interviews).

Weight Variables

Body weight is measured in BMI (kg/m^2), which is calculated from self-reported weight and height at each interview. Five levels of body weight are categorized according to the guidelines provided by World Health Organization (World Health Organization, 2000), including Underweight ($\text{BMI} < 18.5$), Normal Weight ($18.5 \leq \text{BMI} < 25$), Overweight ($25 \leq \text{BMI} < 30$), Class I Obese ($30 \leq \text{BMI} < 35$) and Class II/III Obese ($\text{BMI} \geq 35$). Weight change is measured by the percentage change in BMI between any two consecutive interviews and is classified into five categories: Large Weight Loss (BMI drops by $\geq 10\%$), Small Weight Loss (BMI drops by $[5\%, 10\%]$), Stable Weight

Change (BMI changes by (-5%, 5%)), Small Weight Gain (BMI increases by [5%, 10%)), and Large Weight Gain (BMI increases by $\geq 10\%$). In this analysis, Normal Weight and Stable Weight Change are used as reference groups.

Confounders

A dummy variable for preexisting diseases is constructed using self-reported diagnosis of chronic diseases at each interview. If a respondent answers yes at an interview to any of the questions that ask whether he/she has been told that he/she has one of the five types of chronic disease (diabetes, cancers, lung diseases, heart problems and stroke) ever (for the first interview) or since last interview (for the subsequent interviews), he/she will be marked as having had preexisting diseases. In addition, self-rated health is included to account for unobservable factors that can not be easily measured or diagnosed. The original variable in HRS has five categories (excellent, very good, good, fair and poor) and is re-grouped into two. The first three categories (excellent, very good and good) are combined to indicate good self-rated health, while the other two (fair and poor) are combined to indicate poor self-rated health and used as the reference group.

Three dummy variables are created based on individuals' smoking status, whether one has never smoked or previously smoked or is currently smoking, at each interview. Never smoker is used as the reference group.

In addition, a dummy variable for physical activity and exercise is created based on the frequency of vigorous physical activity. However, since this frequency is

measured differently in the first six and the rest four rounds of interviews, the dummy variable is assigned one if the respondent had vigorous physical activity three or more times a week in the first six interviews, or two or more times a week in the other interviews.

Some time-independent characteristics are adjusted in this analysis as well. Those include gender, age at first interview, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic and Other), education levels (no high school diploma, high school diploma or GED, some college and college degree).

Furthermore, several time-dependent socio-economic (SES) covariates that are measured at both first and subsequent interviews, including marital status (never married, married, divorced or separated, and widowed), and log of household income/wealth are also controlled. All time-dependent covariates that are measured subsequent to baseline are lagged for one interview, in order to ensure these risk factors and weight change line up in the correct order along the causal pathway. On the other hand, time-dependent covariates that are measured at first interview are used as baseline controls in the analytical models.

Methods

As earlier discussed, it is critical to model the association between obesity and mortality dynamically and at the same time properly adjust for the confounding caused by time-varying health conditions and time-varying health behaviors. Because the direct

result of sickness or smoking is weight change rather than having a certain level of body weight, I separate one's BMI measures into two components, a stock measure (baseline BMI) and a flow measure (weight change between any two consecutive interviews), by controlling BMI measured at first interview and modeling time-varying weight change.

In addition, standard regression models fail to yield unbiased estimates of effects of weight change on mortality when there are time-dependent confounders that are predictors of mortality and weight change and that can also be affected by prior weight change. This bias occurs because controlling time-dependent confounders in regression will lead to over-adjustment for the mortality risks of prior weight change and hence produce underestimates of the mortality risks of weight change. I apply a Marginal Structural Model (MSM) that creates a pseudo-population in which the association between weight change and mortality is considered not confounded (Hernán & Robins, 2006; J M Robins et al., 2000). Essentially, MSM is similar to the Propensity Score method, but the latter lacks the capability of generating weights using both baseline and time-varying factors (Hernán & Robins, 2006). The basic idea of MSM is to weight the sample from the observational longitudinal study with the inverse probability of an individual experiencing a certain level of weight change between two interviews conditional on the values of confounders and other covariates. This weighting resembles a randomized experiment where time-dependent weight changes are thought to be assigned to an individual randomly and therefore the confounding by health conditions is eliminated. Specifically, a single weight is generated for each observation during this procedure. The newly created weights are then supplied to models that estimate the

effects of obesity and weight change on mortality. A detailed discussion of the MSM approach used in this paper is presented in the Appendix. All analyses are performed with SAS program Proc Genmod.

Results

Figure 3.1 plots the mean BMI trajectory for a synthetic cohort constructed from the entire sample by baseline BMI levels. For the underweight subsample, continuing increase in body weight is observed. In contrast, the heaviest obese subsample shows continuing weight loss from age 50 to 80. The rest BMI categories display relatively constant weight over years until very old age, namely after 75 years old. In sum, the weight trajectories tend to regress toward the mean. This provides evidence that only looking at baseline weight status may produce biased estimates of the impact of obesity on mortality.

Table 3.1 presents the baseline characteristics from the whole sample by body weight change history over time during the entire study. Overweight people constitutes the largest group (41.31%) of the sample, followed by people with normal weight (33.58%), while Class II/III obese (7.01%) and underweight (1.14%) are observed in only a small proportion of the sample. A large majority (80%) of the sample self-rated their health at baseline as at least good, and 70.81% has never been diagnosed with any of the five types of chronic disease. However, only 35.92% of the sample was free from these chronic diseases through the follow-up years.

Also shown in Table 3.1 is that relative to those who remained of stable weight throughout the study, every type of weight change is more common among current/former smokers, those with less vigorous physical activity, those with worse self-rated health and those with more incidents of chronic disease both prior and during the study.

In order to examine whether pre-existing health conditions are predictors of weight change and mortality, and in the meantime can be predicted by previous weight change so that the time-dependent confounding conditions underlying MSM are satisfied, three pairs of model are estimated. The first pair of models test the hypothesis that weight change can be predicted by pre-existing health conditions, by fitting two multinomial logistic models with categories of weight change (1=large weight loss, 2=small weight loss, 3=stable weight, 4=small weight gain, 5=large weight gain) between survey n ($n \geq 2$) and $n+1$ as dependent variables, both controlling time-varying smoking status as well as demographic and socio-economic covariates, but one (Model A1) includes dummy variable for diagnosis of chronic diseases between $n-1$ and n as an predictor while the other one (Model A0) simply works as a null model. The likelihood ratio test (LR=13.08, $p < 0.01$) of these two models suggests that Model A1 predicts weight change better than the null model. In addition, Model A1 shows that having pre-existing chronic diseases is significantly associated with weight loss (relative risk=1.93, $p < 0.001$).

The second pair of models test whether pre-existing health conditions predict mortality, using Cox hazard models with time-varying covariates that predict the mortality risk. Both models control for baseline weight categories, weight change history,

smoking status, as well as demographic and socio-economic covariates, but one is a null model (Model B0) and the other one (Model B1) includes time-varying dummy variable for diagnosis of chronic diseases. The likelihood ratio test of these two models produces a LR=218.85 ($p<0.001$), and the estimate of the pre-existing chronic disease variable in Model B1 shows an association with higher risk of mortality (hazard ratio=2.43, $p<0.001$) that is statistically significant, indicating pre-existing chronic diseases do predict mortality.

The third pair of models examine whether weight change predicts incidence of chronic diseases. Two logistic models both controlling baseline weight categories, smoking status, as well as demographic and socio-economic covariates, are fitted. Again, one of the two models (Model C1) includes weight change history, while the other one is the null model (Model C0). The likelihood ratio test (LR=157.91, $p<0.001$) suggests that prior weight change does predict incidence of chronic diseases. In addition, weight gains (both small size (odds ratio=1.08, $p<0.01$) and large size (odds ratio=1.26, $p<0.001$)) are associated with excess risk of experiencing chronic disease.

Alternatively, substituting self-reported health conditions for diagnosis of chronic diseases in all the above models yields similar results, indicating that health conditions (both observable and non-observable) indeed operate simultaneously as confounders and mediators along the causal pathway.

Table 3.2 presents the estimated hazard ratios (with 95% confidence intervals) of baseline body weight and time-dependent weight changes between consecutive

interviews, using Marginal Structural Models. Model 1 is a null model that includes only baseline weight status and weight change history. U-shaped and J-shaped association with mortality are observed for baseline weight status and time-dependent weight change respectively. Underweight and Class II/III obese at baseline are associated with excess mortality risks relative to normal weight, while the effects for overweight and Class I obese are not statistically significant. Similarly, large weight loss, small weight loss, and large weight gain are all associated with higher mortality relative to stable weight change.

Model 2 adjusts for socio-demographic and SES characteristics, measured at first interview and follow-up interviews. The estimates from this model change only slightly from those in Model 1. Overall, the hazard ratios for weight change and baseline weight status for all categories decline as expected, as the covariates adjusted tend to have negative associations with weight status and weight change.

Further controlling time-dependent health behavior covariates (smoking and physical activity) in Model 3, I show how these covariates confound the estimates of mortality risks. Inclusion of these covariates leads to increase in hazard ratios for Class II/III obese at baseline, but decrease for other baseline weight categories and all weight change categories except for small weight gain. The amount of physical activity is a time-dependent confounder in this model, as it has impact on future weight status as well as mortality and can be affected by past weight and health status. However, it only has a negligible effect on the estimated hazard ratios (model un-shown). The majority of the change in the estimated hazard ratios between Model 2 and Model 3 is attributable to smoking. On the one hand, because smoking accounts for disproportionate number of

those non-obese and those who have experienced weight loss, failure to control for it will result in underestimate of the mortality risk of obesity and overestimate of the mortality risks of being underweight and weight loss, which is consistent to the results in Model 3. On the other hand, it has been shown that cessation of smoking is likely to lead to weight gain (Carney & Goldberg, 1984; Cook, Shaper, Pocock, & Kussick, 1986; Foy, Bell, Farmer, Goff, & Wagenknecht, 2005; Rimm et al., 1995; Wannamethee, Shaper, & Perry, 2001), hence after including a dummy variable for ever-smokers, the decrease in estimated mortality risk for time-dependent weight gain is not implausible. This result may also be explained by prior studies that find active smoking is a modifiable risk factor of type 2 diabetes which is associated with both large weight gain and increased mortality (Foy et al., 2005; Hu et al., 2001; Manson, Ajani, Liu, Nathan, & Hennekens, 2000; Will, Galuska, Ford, Mokdad, & Calle, 2001).

Model 4 additionally accounts for both diagnosed and underlying health conditions by including time-dependent measurements for diagnose history of chronic diseases and self-rated health respectively. Because the subsample who were underweight at baseline and who have experienced weight loss consist disproportionately individuals with relatively poor health status, it is expected that once health conditions are adjusted the estimated hazard ratios for weight loss and underweight at baseline will decline, while effects of obesity and weight gain will increase. The results in Model 4 confirm this expectation.

Overall, the estimates produced in Model 4 are consistent with existing literature. With reference to normal weight, underweight and Class II/III at baseline are associated

with hazard ratios that are 2.0 and 1.8 respectively, whereas overweight and Class I obesity do not significantly lower or raise the mortality risks. Furthermore, relative to stable weight change, all types of weight change lead to significantly increased risk of mortality. Specifically, large weight loss results in a mortality risk that is nearly four times of staying in the stable weight range and small weight loss is about 1.8 times riskier. In contrast, large weight gain and small weight gain are associated with hazard ratios that are 2.0 and 1.2 respectively. These large hazard ratios indicate that weight change has stronger effects on mortality than baseline BMI.

Alternatively, changes in BMI units are used in the MSMs instead of the percentage changes in body weight, as some may argue that changes in BMI units directly reflect the variations in dietary intake. In this case, weight change is classified into five categories based on the magnitude of change in BMI units: Large Weight Loss (BMI drops by over 3 units), Small Weight Loss (BMI drops by 0.5-3 units), Stable Weight Change (BMI changes by (-0.5, 0.5) unit), Small Weight Gain (BMI increases by 0.5-3 units), and Large Weight Gain (BMI increases by over 3 units). Using this alternative measurement for weight change does not lead to substantial change in the estimated effects of weight change and baseline weight status on mortality. The results for this exercise are shown on Table A1 in Appendix 2.

One underlying assumption of Model 3 and Model 4 is that the statistical confounding by smoking and health status are independent. However, in fact, they are closely associated with each other, as smoking raises the risks of developing various chronic diseases that result in weight loss. I repeat Model 4 with subsamples split by

smoking status, accounting for the fact that the reverse causation is greater among smokers. Table 3.3 presents the results of this subsample analysis, confirming the disparity of mortality risks among ever-smokers and never-smokers. In general, ever-smokers have higher risk of dying from weight loss and underweight. The mortality risk for being underweight at baseline is over twice as great among ever-smokers than among never-smokers. Also, never-smokers are subject to higher mortality for Class II/III obesity at baseline, but lower mortality for large weight gain. This is consistent with the change in results from Model 2 to Model 3 in Table 3.2 where smoking status is adjusted for. Moreover, the estimates for ever-smokers are further apart from those of Model 4 in Table 3.2, indicating the impact of reverse causation associated with health status is greater among ever-smokers compared to never-smokers.

In order to demonstrate how standard regression models bias the estimates, I repeated the analyses presented in Table 3.2, using Cox hazard model with time-dependent covariates. Results are presented in Table 3.4. Compared to its MSM counterpart, Model 1 estimated using Cox model has a considerably smaller hazard ratio for large weight loss. This is very likely because the MSMs take into account the dependency that between weight changes during consecutive survey windows and that between weight changes and baseline weight status, while the Cox models do not. To test this hypothesis, I regress weight change between survey n ($n \geq 2$) and survey $n+1$ on baseline weight status and weight change between survey $n-1$ and survey n . The estimates suggest prior weight gain and being at least Class I obese at baseline are associated with higher chances of weight loss at a later time. In contrast, prior weight loss is associated

with future weight gain. This is consistent with Figure 3.1 which shows body weight trajectory tends to regress toward the mean that is associated with lower mortality. As a result, failing to account for these dependencies incline to lead to underestimates of the mortality risks of both weight change and baseline weight status, especially for the extreme body weight levels.

Similar to the MSM, the estimates from Model 2 using Cox model change only slightly from those in model 1. Overall, the hazard ratios for weight change and baseline weight status for all categories decline as expected, as the covariates adjusted tend to have negative associations with weight status and weight change. Adding health behaviors in the Cox model yields similar changes in the estimated hazard ratios as it does for the MSM. Comparing to Model 2, Model 3 shows increase in hazard ratios for Class II/III obese at baseline, but decrease for other baseline weight categories and all weight change categories.

Model 4 additionally adjusts for confounding by health conditions. It is expected that the estimated hazard ratios for weight loss and being underweight at baseline will decline, while effects of obesity and weight gain will increase. In fact, although the effects of weight loss and being underweight at baseline on mortality decline as expected, the effects of weight gain and being Class II/III obesity at baseline on mortality drop by 4% and over 25% respectively. This is because the Cox hazard model fails to produce unbiased estimates when the time-dependent confounder in this model, health conditions, is simultaneously 1) predicted by past weight or weight change history, 2) a predictor of future weight change and mortality. Simply including time-dependent health status in the

Cox model will lead to over-adjustment for the effects of baseline weight status, as time-dependent health status after baseline operates as a mediator between baseline weight status and mortality. This explains why the effect of being Class II/III obese at baseline drops by 25.5% from Model 3 to Model 4. Similarly, the over-adjustment could be the reason of the slight decline in the effects of large weight gain as well. In contrast, the MSM includes the time-dependent health condition covariates only in the re-weighting models that calculate the probability a respondent experiencing a certain level of weight change or being censored at a certain time-point, but not in the model to which the new weights are supplied to calculate the direct effects of weight change and baseline weight status on mortality. Consequently, the MSM is free from the over-adjustment problem and produce unbiased estimates for the direct causal effects of weight change and baseline weight status on mortality. In sum, the comparison between Model 4 using MSM and Cox model demonstrates that MSM is the appropriate model to apply when health status operates as a time-dependent confounder. In fact, the estimates produced in Model 4 using MSM are consistent with existing literature.

The analysis for Model 4 in Table 3.2 is also repeated with subsamples split by baseline weight status. Results are shown in Table 3.5. Large weight loss is associated with excess mortality across all weight categories, while large weight gain is an indicator of increased mortality for those who have at least normal weight. Small weight loss is also found to be associated with higher mortality risk for people in normal and overweight range at baseline. And small weight gain increases mortality risk for those who are above Class I obese. The significance of these estimates varies as a result of

smaller sample size, but overall the estimated effects of weight change on mortality in this analysis are consistent with estimates from the whole sample, except for the underweight group which now appears benefit from weight gain. The estimates from this analysis are in general also consistent with Myrskylä and Chang (2009) who use quadratic terms of BMI and weight change measured by the number of units of change in BMI from only the first two interviews. But this present study also shows that weight change will be associated with excess mortality risk for more groups of people depending on their baseline weight status and scale of weight change.

Sensitivity Analyses

I perform sensitivity analyses to test the robustness of the associations between time-dependent weight change as well as baseline weight status and mortality estimated above, by applying alternative sample- and model- specifications. The remaining parts of the models other than the altered parts are kept unchanged. The results are displayed in Table 3.6, and are compared with Model 4 in Table 3.2, the main model.

Model SA1 restricts the sample to subjects that were free from any of the five types of chronic diseases in all interviews they have participated. This restriction ends up with keeping only 3,117 subjects, 21,319 observations and 319 deaths from the original sample. The estimates of hazard ratios for weight gain and being overweight or above at baseline remain relatively constant from the main model, while the estimated effects of

weight loss and being underweight at baseline decline but still are associated with increased mortality. Some hazard ratios lose significance in this analysis.

Model SA2 restricts the sample to subjects that have rated their health status as at least good in all surveys they participated. This restriction strategy aims to obtain a subsample that is subject to minimum unobservable confounders and it produces a total of 4,219 subjects (30,168 observations) among which only 377 were observed death. Both small and large weight loss remains to be associated with excess mortality. Class II/III obese at baseline is now associated with only slightly lower mortality risk relative to the model with the whole sample, while the effects of other three weight categories lose significance but their point estimates do not change much.

The third sensitivity analysis limits the sample to never smokers at baseline that remained non-smokers until death or dropping off the study (identical to column 2 in Table 3.3). After exclusion of current and former smokers, the number of observations drops to 23,823 and the number of respondents reduces to 3,195, among whom 346 died. The basic associations continue to exist. As smokers are more likely to be leaner and to die, excluding this group would presumably yield larger hazard ratio for obesity but lower hazard ratio for underweight. It is confirmed by the estimates from this model.

Given that people tend to lose weight during the years closer to death due to illness, the fourth sensitivity analysis attempts to find out how the results would change if this bias is minimized by excluding individuals those died within eight years (four follow-up interviews) after their first interview. Since those who lost weight due to severe

illness tend to die in a much shorter period (1-3 years), this restriction using eight years will yield more conservative estimates. This leaves 7,073 respondents, 56,892 observations and 1,145 deaths. All changes in point estimates of hazard ratios are in general considerably small, as regard to the main model. Nevertheless, it is worth to notice that the mortality risk associated with Class I obese becomes statistically significant, and its magnitude increases as expected.

The fifth model uses a quadratic measure instead of dummy variables for BMI measures. As the estimates in previous models, the alternative quadratic BMI measures also show a U-Shaped association with mortality. Again, the hazard ratios associated with time-dependent weight changes remain relatively constant in all categories, compared to the main model.

Overall, the sensitivity analyses suggest the associations observed from the main model is fairly robust, and all results are consistent with the finding that being underweight and class II/III obese at baseline, as well as weight change in all directions are associated with increased mortality risk, relative to the reference groups. Although variations in estimates of hazard ratios are observed in some cases, they are not unacceptably large. And this variation is most likely due to much smaller sample sizes which lead to less precise estimates and loss of statistical power.

Discussion

In this study, the confounding by health behaviors and health conditions is adjusted in a time-dependent manner along the causal pathway through application of marginal structural models. As expected, the findings demonstrate that both the confounding by health behaviors and by health conditions lead to overestimates of the effects of being underweight at baseline and of weight loss, but underestimates the effect of being obese at baseline. These results confirm the hypothesis that smoking and sickness often induce low weight and weight loss (Katherine M Flegal et al., 2013; S. H. Preston et al., 2013; Willett, Dietz, & Colditz, 1999), and as a result bias estimates of the mortality effects of obesity and weight change. In addition, subsample analysis demonstrates that the confounding by poor health conditions has greater impact on smokers than never-smokers, as smoking is associated with excess risks of developing many chronic diseases which may in turn lead to weight loss and higher mortality.

A major strength of this study is addressing the interrelated association between health conditions and weight change in a dynamic framework, while controlling baseline weight status. It is shown that although being underweight or Class II/III obese at baseline is associated with excess mortality risk, being overweight or moderate obese is not. On the other hand, relative to stable weight change, all other levels of weight change significantly raise mortality risk. The association is J-shaped, with large weight loss being nearly twice as riskier as large weight gain. These results are consistent with Mikkelsen et al (1999) who find both weight level and weight change have independent U-shaped associations with mortality, adjusting for smoking and excluding individuals with

preexisting and subclinical diseases. Also, compared to BMI measured at baseline, weight change over time is indeed a stronger predictor of mortality.

The J-shaped association is generally preserved in subsample analyses by initial weight status. This seems to be in contrary to the hypothesis that weight loss for obese or overweight individuals is associated with decreased mortality risk, relative to their initial weight status. However, given that the reference group contains weight loss under 5%, these results are not inconsistent with prior studies (Myrskylä & Chang, 2009). In addition, several observational studies have shown that even voluntary weight loss, such as dieting and exercise, may be associated with increased mortality even for those who are overweight (Arnold, Newman, Cushman, Ding, & Kritchevsky, 2010; French, Jeffery, Folsom, Williamson, & Byers, 1995; Manson et al., 2000; Newman et al., 2001). Also, many practices for losing weight such as diet drug, fasting and smoking are known to have adverse effect. Moreover, anorexia due to aging is likely to be reflected by reduced dietary intake and impaired ability to maintain energy balance among older adults. Accordingly, failing to maintain weight at a stable level may indicate poor homeostatic control, which may be associated with functional impairment and mortality, and may form a tendency of more weight loss among unhealthy people, leading to increased mortality risk (Arnold et al., 2010; Newman et al., 2001). In contrast, large weight gain is associated with increased mortality only for those at or above overweight level, and small weight gain increases mortality only for those who are at least Class I obese. This is supported by physiological studies that find weight gain can be attributable to sedative lifestyle and therefore is associated with cardiovascular problems. Weight gain

may also cause impairment in pulmonary functions that makes breathing difficult (Arnold et al., 2010; Newman et al., 2001). As shown in Table 3.1, there is much larger proportion of underweight or normal weight people losing weight than the proportion of obese people gaining weight, thus more concerns should be paid to weight loss.

The present study has several limitations. First, BMI measures are constructed by self-reported heights and weights, which are found to often underestimate BMI in prior studies (Ezzati, Martin, Skjold, Vander Hoorn, & Murray, 2006), although strong correlation between self-reported and clinically measured BMI have been found in many studies (Myrskylä & Chang, 2009; Willett WC, 1998). Second, heterogeneity in mortality related to weight change may exist across different diseases. Despite the fact that HRS provides diagnosis history for many diseases, without information on cause of death it is unreasonable to infer deaths are caused by a certain type of diagnosed disease. Third, the HRS does not provide measures for historical body weight, such as BMI at age 25 or maximum weight observed; therefore it is impossible to investigate the mortality risk of younger age obesity. Fourth, although the marginal structural model can minimize biases introduced by time-dependent observable confounders, it still demands appropriate model specifications and, as other statistical approaches, it cannot deal with unobservable confounders.

In summary, after addressing some of the concerns in the literature by applying a time-dependent causal model, the findings from this present study suggest that BMI at baseline has a U-shaped association with mortality among elderlies. Additionally, adverse effects are shown for weight change larger than 5% of prior body weight. Future research

may investigate the association between obesity and cause-specific mortality, adjusting for confounding by specific types of disease, as some diseases (e.g. diabetes) are more prone to be related to obesity.

Table 3.1: 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)
Death (%)	20.29	27.00	18.57	22.91	15.73	18.74
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.
Individuals can appear in multiple weight change categories.

Table 3.1 (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.
Individuals can appear in multiple weight change categories.

Table 3.2: Adjusted Effects of Baseline BMI and Weight Change Over Time on Mortality, Marginal Structural Models

Parameter	Model 1	Model 2	Model 3	Model 4
Weight Loss 10%+	4.68 *** (4.058,5.396)	4.673 *** (4.036,5.409)	4.292 *** (3.683,5.161)	3.863 *** (3.258,4.580)
Weight Loss 5-10%	2.066 *** (1.798,2.374)	2.001 *** (1.738,2.304)	1.936 *** (1.674,2.238)	1.81 *** (1.551,2.112)
Weight Gain 5-10%	1.143 . (0.978,1.336)	1.075 (0.903,1.376)	1.181 * (1.005,1.387)	1.196 * (1.017,1.405)
Weight Gain 10%+	1.882 *** (1.571,2.255)	1.816 *** (1.496,2.202)	1.751 *** (1.446,2.12)	1.977 *** (1.667,2.345)
Underweight	2.715 *** (1.908,3.862)	2.634 *** (1.731,3.96)	2.383 *** (1.578,3.599)	2.074 *** (1.277,3.368)
Overweight	0.989 . (0.884,1.107)	0.874 * (0.778,0.982)	0.94 . (0.833,1.061)	0.907 . (0.80,1.028)
Obese I	1.017 . (0.885,1.168)	0.936 . (0.811,1.079)	1.046 . (0.902,1.213)	1.144 . (0.99,1.322)
Obese II/III	1.49 *** (1.258,1.765)	1.421 *** (1.194,1.692)	1.718 *** (1.434,2.059)	1.824 *** (1.539,2.162)

Notes:

Model 1: Includes only baseline weight status and time-dependent weight change.

Model 2: Adds SES and socio-demographic covariates (both baseline and time-varying).

Model 3: Adds confounding by time-dependent health behaviors.

Model 4: Adds confounding by time-dependent health conditions.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 3.3: Adjusted Effects of Baseline BMI and Weight Change Over Time on Mortality, Marginal Structural Models by Smoking Status

Parameter	Ever-Smokers (N=5,483)	Never-Smokers (N=3,195)
Weight Loss 10%+	4.089 *** (3.032,5.472)	3.754 *** (3.047,4.606)
Weight Loss 5-10%	1.976 *** (1.52,2.562)	1.723 *** (1.423,2.081)
Weight Gain 5-10%	1.431 ** (1.106,1.851)	1.079 . (0.877,1.327)
Weight Gain 10%+	2.116 *** (1.568,2.885)	1.904 *** (1.55,2.349)
Underweight	4.229 *** (2.019,8.545)	1.846 *** (1.082,3.033)
Overweight	0.959 . (0.761,1.207)	0.881 . (0.758,1.024)
Obese I	1.089 . (0.891,1.337)	1.011 . (0.888,1.154)
Obese II/III	1.738 ** (1.292,2.35)	1.894 *** (1.535,2.342)

Notes: Both models are built on Marginal Structural Model that includes covariates for SES and socio-demographic characteristics (gender, age at first interview, race/ethnicity, education, and household income), covariates for health behaviors (physical activity), and covariates for health conditions (previous diagnosis of chronic diseases and self-rated health conditions)

* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 3.4: Adjusted Effects of Baseline BMI and Weight Change Over Time on Mortality, Cox Hazard Models with Time-Varying Covariates

Parameter	Model 1	Model 2	Model 3	Model 4
Weight Loss 10%+	3.946 *** (3.349,4.65)	3.84 *** (3.257,4.527)	3.522 *** (2.985,4.156)	3.102 *** (2.627,3.662)
Weight Loss 5-10%	2.012 *** (1.721,2.352)	1.952 *** (1.669,2.283)	1.845 *** (1.576,2.161)	1.721 *** (1.469,2.015)
Weight Gain 5-10%	1.21 * (1.017,1.441)	1.216 * (1.021,1.449)	1.181 . (0.991,1.407)	1.151 . (0.966,1.372)
Weight Gain 10%+	1.831 *** (1.488,2.253)	1.798 *** (1.46,2.214)	1.631 *** (1.323,2.012)	1.552 *** (1.277,1.892)
Underweight	2.414 *** (1.571,3.71)	2.32 *** (1.502,3.585)	1.826 ** (1.168,2.854)	1.748 * (1.119,2.732)
Overweight	1.031 . (0.904,1.176)	0.921 . (0.806,1.053)	0.962 . (0.841,1.1)	0.916 . (0.801,1.048)
Obese I	1.138 . (0.97,1.335)	1.022 . (0.87,1.201)	1.111 . (0.943,1.31)	0.973 . (0.825,1.148)
Obese II/III	1.375 *** (1.08,1.734)	1.295 *** (1.029,1.619)	1.691 *** (1.384,2.066)	1.259 * (1.028,1.542)

Notes:

Model 1: Includes only baseline weight status and time-dependent weight change.

Model 2: Adds SES and socio-demographic covariates (both baseline and time-varying).

Model 3: Adds confounding by time-dependent health behaviors.

Model 4: Adds confounding by time-dependent health conditions.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 3.5: Marginal Structural Models by Baseline Weight Status

Parameter	Underweight	Normal	Overweight	Class I Obese	Class II/III Obese
Weight Loss 10%+	2.65 ** (1.40,5.03)	2.31 ** (1.32,4.05)	4.09 *** (3.10,5.40)	4.16 *** (3.29,5.25)	4.60 *** (2.59,8.05)
Weight Loss 5-10%	1.03 (0.50,2.10)	1.42* (1.11,2.09)	1.84 *** (1.45,2.34)	1.34 (0.93,1.96)	1.45 (0.87,2.44)
Weight Gain 5-10%	0.52 (0.11,2.45)	1.20 (0.84,1.71)	1.06 (0.81,1.39)	1.77 *** (1.30,2.41)	1.13 *** (0.73,1.74)
Weight Gain 10%+	0.89 (0.15,5.27)	1.47 (0.97,2.22)	1.75 ** (1.23,2.50)	3.02 *** (1.99,4.58)	2.45 ** (1.81,3.90)

Notes: All models are based on Model 4 in Table 2.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 3.6: Sensitivity Analyses

Parameter	Main	SA1	SA2	SA3	SA4	SA5
BMI Square						1.01 *** (1.00,1.01)
BMI						0.75 *** (0.71,0.79)
Weight Loss 10%+	3.86 *** (3.26,4.58)	3.13 *** (2.10,4.68)	3.12 *** (2.14,4.56)	3.75 *** (3.05,4.61)	4.22 *** (3.45,5.14)	3.84 *** (3.28,4.48)
Weight Loss 5-10%	1.81 *** (1.55,2.11)	1.57 ** (1.12,2.19)	1.70 *** (1.26,2.29)	1.72 *** (1.42,2.08)	1.96 *** (1.64,2.34)	1.80 *** (1.55,2.08)
Weight Gain 5-10%	1.20 * (1.02,1.41)	1.15 (0.83,1.61)	1.07 (0.79,1.45)	1.08 . (0.88,1.33)	1.18 . (0.96,1.45)	1.29 ** (1.09,1.52)
Weight Gain 10%+	1.98 *** (1.67,2.35)	1.89 * (1.58,2.26)	1.09 (0.66,1.80)	1.90 *** (1.55,2.35)	1.77 *** (1.40,2.24)	1.91 *** (1.57,2.33)
Underweight	2.07 *** (1.28,3.37)	1.84 (0.76,4.47)	1.88 (0.62,5.67)	1.85 *** (1.08,3.03)	1.94 * (1.05,3.57)	
Overweight	0.91 . (0.80,1.03)	0.85 (0.66,1.09)	0.91 (0.72,1.15)	0.88 . (0.76,1.02)	1.07 . (0.92,1.24)	
Obese I	1.14 (0.99,1.32)	1.03 (0.73,1.44)	1.21 (0.90,1.63)	1.01 (0.89,1.15)	1.31 ** (1.10,1.57)	
Obese II/III	1.82 *** (1.54,2.16)	1.68 (0.96,2.95)	1.80 ** (1.250,2.74)	1.89 *** (1.54,2.34)	1.90 *** (1.52,2.38)	

Notes:

Main: Refers to Model 4 in Table 2.

SA1: Sample is restricted to subjects that were free from any of the five types of chronic diseases in all interviews.

SA2: Sample is restricted to subjects that have rated their health status as at least good in all interviews.

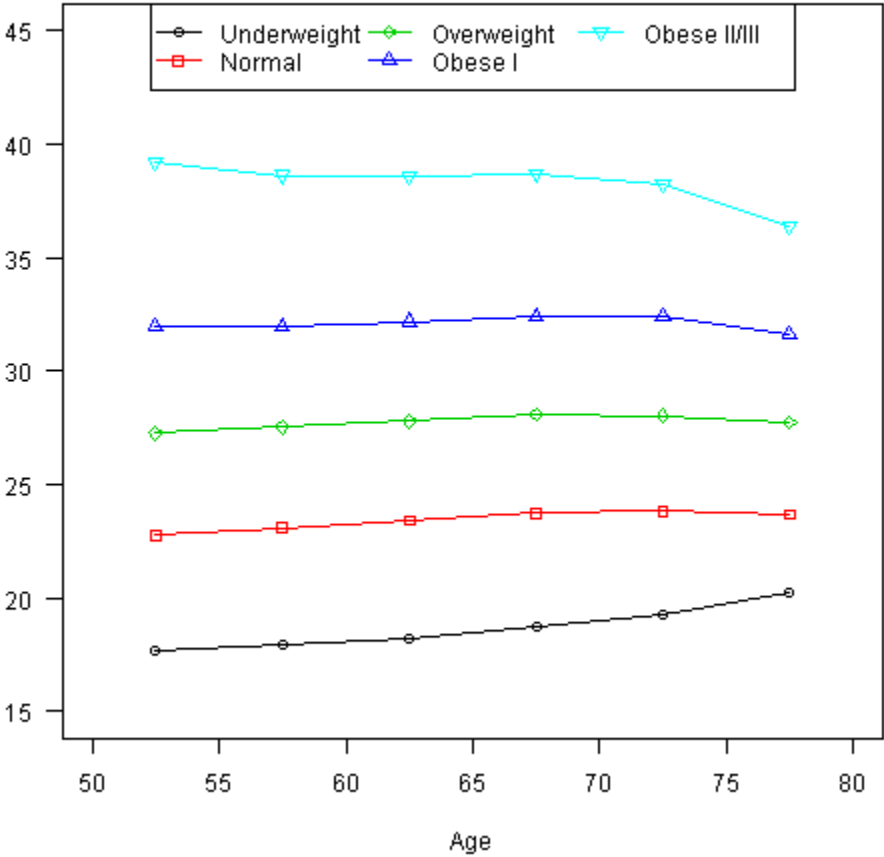
SA3: Sample is restricted to never smokers at baseline that remained non-smokers in all interviews.

SA4: Excludes individuals those died within eight years (four follow-up interviews) after their first interview.

SA5: Use quadratic BMI measures for baseline weight status.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Figure 3.1: Mean BMI Trajectory by Baseline BMI Levels



Appendices

Appendix 1

Let $M_{x,t}$ be the matrix of the instantaneous transition rates between different health states at age x and time t . The element in the i th row and j th column therefore indicates the transition rate that an individual aged x at time t in the i th state will move into the j th state instantaneously. For this particular study,

$$M_{x,t} = \begin{pmatrix} m_{x,t}^{HU} + m_{x,t}^{HD} & -m_{x,t}^{UH} \\ -m_{x,t}^{HU} & m_{x,t}^{UH} + m_{x,t}^{UD} \end{pmatrix}$$

Similarly, the matrix of the probability an individual aged x at time t in the i th state will transit into the j th state within a one-year interval can be written as:

$$Q_{x,t} = \begin{pmatrix} 1 - (q_{x,t}^{HU} + q_{x,t}^{HD}) & q_{x,t}^{UH} \\ q_{x,t}^{HU} & 1 - (q_{x,t}^{UH} + q_{x,t}^{UD}) \end{pmatrix}$$

Assuming the distributions of the transitions are linear with age and all transitions occur at exact the middle of the one-year interval, a relationship between $M_{x,t}$ and $Q_{x,t}$ can be established,

$$Q_{x,t} = \frac{I - \frac{M_{x,t}}{2}}{I + \frac{M_{x,t}}{2}}$$

where I is an identity matrix.

The transition probabilities between specific health states can be converted as below, given the assumption of no recovery from disabled to non-disabled,

$$q_{x,t}^{HU} = \frac{m_{x,t}^{HU}}{\left(1 + \frac{m_{x,t}^{HU}}{2} + \frac{m_{x,t}^{HD}}{2}\right)\left(1 + \frac{m_{x,t}^{UD}}{2}\right)}$$

$$q_{x,t}^{UD} = \frac{m_{x,t}^{UD}}{1 + \frac{m_{x,t}^{UD}}{2}}$$

$$q_{x,t}^{HD} = \frac{m_{x,t}^{HU} + m_{x,t}^{HD}}{\left(1 + \frac{m_{x,t}^{HU}}{2} + \frac{m_{x,t}^{HD}}{2}\right)} - q_{x,t}^{HU}$$

Let $l_{x,t}$ denote the matrix of number of persons alive at age x and time t in different health states, and $l_{x,t} = \begin{bmatrix} l_{x,t}^H \\ l_{x,t}^U \end{bmatrix}$.

Accordingly, the number of people alive one year later is

$$l_{x+1,t+1} = \begin{bmatrix} l_{x+1,t+1}^H \\ l_{x+1,t+1}^U \end{bmatrix} = \begin{bmatrix} l_{x,t}^H (1 - q_{x,t}^{HU} - q_{x,t}^{HD}) \\ l_{x,t}^U (1 - q_{x,t}^{UD}) + l_{x,t}^H q_{x,t}^{HU} \end{bmatrix}$$

Next, person-years lived by people aged x alive at time t by health status can be estimated by

$$L_{x,t} = \begin{bmatrix} \frac{l_{x,t}^H + l_{x+1,t+1}^H}{2} \\ \frac{l_{x,t}^U + l_{x+1,t+1}^U}{2} \end{bmatrix}$$

The cumulative persons-years lived by individuals aged x alive at time t is

$$T_{x,t} = \begin{bmatrix} T_{x,t}^{ND} \\ T_{x,t}^D \end{bmatrix} = \sum_{a=x}^{85} L_{a,t}$$

Finally, LE^{ND} and LE^D as well as the total LE at age x and time t are calculated as below

$$LE_{x,t}^{ND} = \frac{T_{x,t}^{ND}}{l_{x,t}}$$

$$LE_{x,t}^D = \frac{T_{x,t}^D}{l_{x,t}}$$

$$LE_{x,t} = LE_{x,t}^{ND} + LE_{x,t}^D$$

Appendix 2

In this paper, the association between body weight change and mortality is modeled in a dynamic way. Not only individuals' body weights tend to vary over time, the association is also likely to be confounded or mediated by both observable and unobservable time-dependent confounders. For instance, the development of chronic diseases is possibly a consequence of prior weight gain and could lead to both subsequent weight loss and mortality. And the confounding caused by chronic diseases could be more complicated when time-dependent health-related behavior, such as smoking, drinking and exercise, are taken in to account. Diagram A2 demonstrates a complex causal pathway, given that $\Delta W(t)$ denotes the individual's exposure (change in body weight) between time t and $t+1$, $O(t)$ and $U(t)$ denote all observable (e.g. diagnosed diseases) and unobservable confounders at time t respectively, where $O(t)$ and $U(t)$ temporally precede $\Delta W(t)$, and D stands for the final outcome (mortality). As shown in the diagram, one's body weight change at a certain time point could influence his/her mortality through both direct and indirect causal pathways along the timeline, and this relation is subject to both observable and unobservable confounding from earlier time periods. In addition, one's current body weight change could be influenced by the past changes.

However, conventional regression approaches that estimate the direct effects of change in weight on mortality yield biased estimates when there are time-dependent confounders, such as some chronic diseases, which are influenced by previous weight change, even if these confounders are adjusted in regression models. Consequently,

adopting an appropriate model that accounts for the variations of body weight over time and adjusts for time-dependent confounding is essential in this study.

Suppose the association between weight change and mortality is not biased by either observable or unobservable confounders, then the effects of weight change on mortality can be considered causal and direct. In other words, not only there is no history of unobservable confounders $U(0), U(1), U(2), \dots, U(t-1)$, and $U(t)$, at each time point t , one's past weight change history $\Delta W(1), \Delta W(2), \dots, \Delta W(t)$ is also not associated with the history of measured confounders $O(1), O(2), \dots, O(t)$. To simplify the model, let us assume there is only one data point for each individual. The primary goal is to estimate the adjusted direct effect of experiencing a certain level of weight change (ΔW_i) on mortality outcome (D_i) for individual i after sufficiently adjusted for all confounders and risk factors (O_i) including health conditions and health behaviors, assuming there is no other unobservable confounder. In this case, the probability for individual falling into different weight change categories (large weight loss, small weight loss, stable weight change, small weight gain, and large weight gain) would be the same, as if an individual is assigned the amount of weight change randomly in an experiment. This being assumed, one can use the risk ratios to measure the casual effect of one's weight change being at a certain level as opposed to being at another level on mortality. Let $D_i(\Delta w)$ denote the counterfactual mortality outcome of individual i if his level of weight change is set to $\Delta W_i = \Delta w$. The risk ratio that compares mortality for this counterfactual outcome to mortality observed at level $\Delta W_i = \Delta w^*$ can be written as $RR(\Delta w, \Delta w^*) = \frac{P(D_i(\Delta w) = 1)}{P(D_i(\Delta w^*) = 1)}$, where $P(D_i(\Delta w) = 1)$ and $P(D_i(\Delta w^*) = 1)$, are the probabilities that an individual dies

given the levels of weight change are Δw and Δw^* respectively. This risk ratio can be estimated by fitting a log-linear model as below using the observed data

$$\log[P(D_i = 1 | \Delta W_i = \Delta w_i)] = \beta_0 + \beta_1 \Delta W_i$$

where Δw_i represents the observed weight change for individual i . The parameter β_1 gives an unbiased estimate of the direct causal effect of weight change on mortality, given the assumption so far is that confounders do not exist.

However, since the association between weight change and mortality is in fact confounded, the above model will fail to produce an unbiased estimate and the probability of an individual having a certain level of weight change will be conditional on the confounders. To adjust the bias, a pseudo-population, in which individuals' weight changes are uniformly distributed with equal probability as if they are randomly assigned, can be created by applying a weight that is the inverse of the probability of one's weight change being at a certain level conditional on his/her vector of all confounders and other relevant covariates as observed in the data set, again assuming all confounders can be adjusted using information provided by the observational dataset and unobservable

confounders do not exist. The weight can be expressed as $wt_i = \frac{1}{P(\Delta W_i = \Delta w_i | O_i = o_i)}$,

where Δw_i and o_i are observed weight change and observed confounders and other relevant covariates for individual i . This weight can be estimated from observed data using logistic regression for ΔW with binomial values, multinomial logistic regression for ΔW with multi-level values, and ordinary linear regression for ΔW with continuous values. The corresponding function form of ΔW will be on the left-hand side of the

equation as the dependent variable and the vector of O will be on the right-hand side of the equation as a set of independent variables.

This idea of weighting described above can be extended to a Marginal Structural Model (James M Robins, 1998; Robins JM, 1999) which can be applied to longitudinal dataset. In essential, Marginal Structural Model (MSM) is a weighted longitudinal analysis. It treats the exposure/ treatment, in this case the levels of weight change, as a time-dependent covariate. For this study, the key idea therefore is to conduct survival analyses with a set of weights that have been calculated for each individual at each interview.

A typical Cox proportional hazard model with time-dependent treatment variables but no time-dependent confounders is expressed in the form of:

$$h(t | \Delta \bar{W}(t), V) = h_0(t)(\partial_1 \Delta W(t) + \partial_2 V)$$

Where $\Delta \bar{W}(t)$ represents the observed history of one's weight change over time up to time t (the overbar notation is also adopted for time-dependent confounders $O(t)$), and V represents one's observed time-independent characteristics at baseline, such as gender, race and age at baseline, that do not vary over time, and $h_0(t)$ is the unspecified underlying hazard. When time-dependent confounders are not absent, particularly when the time-dependent confounders are both influenced by prior weight changes and are predictors for the subsequent weight changes and final mortality outcome, the causal effect of weight change on mortality will be biased (Hernán & Robins, 2006; J M Robins et al., 2000). In order to correctly adjust for the time-dependent confounders and obtain unbiased causal effect estimates, appropriate weights need to be applied in estimating

parameters in the hazard function. Parameters estimated using MSM are called inverse-probability-of-treatment-weighted (IPTW) estimators. However, because the conditional probability of having a certain level of weight change $P(\Delta W_i = \Delta w_i | O_i = o_i)$ may have large variations when time-dependent confounders O_i are strongly associated with ΔW_i , large weights may be produced for some observations and make the weighted analysis dominated by these observations. Therefore, instead of using the inverse of the conditional probability of the treatment, *Robins et al. (2000)* proposes to use “stabilized” weights that can reduce the variations of the IPTW estimators by replacing the numerator, 1, with the conditional probability of having a certain level of weight change conditional on weight change history and time-independent characteristics. For subject i , the stabilized weights at time t is

$$sw_i(t) = \prod_{k=0}^t \frac{P(\Delta W_i(k) = \Delta w_i(k) | \Delta \bar{W}_i(k-1) = \Delta \bar{w}_i(k-1), V_i = v_i)}{P(\Delta W_i(k) = \Delta w_i(k) | \Delta \bar{W}_i(k-1) = \Delta \bar{w}_i(k-1), \bar{O}_i(k) = \bar{o}_i(k))}$$

where k is an integer that denotes the number of corresponding time unit (day, month, year, etc). The maximum value of k is the integer less or equal to time t .

$\Delta \bar{W}_i(k-1) = (\Delta W_i(0), \Delta W_i(1), \dots, \Delta W_i(k-1))$, represents the subject’s entire weight change history up to the $(k-1)$ th time unit, and $\bar{O}_i(k) = (O_i(1), O_i(2), \dots, O_i(k))$, denotes subject i ’s entire history of time-dependent observable risk factors including time-dependent confounders up to the k th time unit. V_i denotes one’s time-independent characteristics at baseline and is contained in $O_i(1)$.

One special feature for longitudinal observational datasets is that not every subject’s final outcome is observed. Censoring by loss to follow-up often occurs when

the subject drops from the study or when the end of the study has been reached. In order to create a pseudo-population that takes into account not only confounding but also loss to follow-up to make the estimates of the direct causal effect unbiased, censoring has to be adjusted by introducing an additional set of weights. Let $C_i(k)=1$ indicates that the subject i is lost to follow-up at the k th time unit and $C_i(k)=0$ otherwise, the weights can be then expressed as:

$$sw_i^C(t) = \prod_{k=0}^t \frac{P(C_i(k)=0 | \bar{C}_i(k-1)=0, \Delta\bar{W}_i(k-1)=\Delta w_i(k-1), V_i=v_i)}{P(C_i(k)=0 | \bar{C}_i(k-1)=0, \Delta\bar{W}_i(k-1)=\Delta w_i(k-1), \bar{O}_i(k)=\bar{o}_i(k))}$$

Finally, the two weights are multiplied together to get the final weights which will then be used in the models that estimate the direct effects. Hence, for subject i , the weight at time t is $wgt_i(t) = sw_i(t) * sw_i^C(t)$. Each of the two multiplier weights can be estimated using pooled logistic regression (J M Robins et al., 2000) that treats each person-time unit as an individual observation.

The last step is to estimate the direct effect of weight change on mortality using a hazard model that incorporates the above weight. However, most statistical packages for estimating Cox proportional model do not support weights that vary over time. One way to circumvent this is to apply weighted pooled logistic regression which has been proved to be equivalent to Cox proportional hazard model (D'Agostino et al., 1990), controlling for baseline hazard and baseline covariates. Let $D_i(k)=1$ represents that subject i died by the k th time unit, and $D_i(k)=0$ otherwise, the pooled logistic regression can be written as:

$$\text{Logit } P[D_i(k) = 1 | D_i(k-1) = 0, \bar{A}_i(k-1) = \bar{a}_i(k-1), V_i = v_i] = \lambda_0(k) + \lambda_1 * A_i(k-1) + \lambda_2 V_i$$

where $\lambda_0(k)$ is the unspecified baseline hazard at the k th time unit, λ_1 is the coefficient vector for the degrees of weight change, and λ_2 is the coefficient vector for the baseline covariates. The hazard ratio can be obtained by simply taking the exponent of corresponding coefficients. Time-dependent confounders have already contributed in calculating the stabilized weights and therefore are not included in the final model, in order to avoid the over-adjustment problem. The above models for estimating weights and the direct effects of weight change on mortality can be fitted with SAS Proc Genmod.

Table A1: Adjusted Effects of Baseline BMI and Weight Change in BMI Unit Over Time on Mortality Marginal Structural Models

Parameter	Model 1	Model 2	Model 3	Model 4
Weight Loss 3+ Units	4.661 *** (3.901,5.568)	4.646 *** (3.876,5.569)	4.219 *** (3.494,5.093)	3.964 *** (3.283,4.787)
Weight Loss 0.5-3 Units	1.87 *** (1.637,2.135)	1.824 *** (1.596,2.085)	1.769 *** (1.542,2.031)	1.719 *** (1.499,1.97)
Weight Gain 0.5-3 Units	1.168 (1.02,1.338)	1.192 (1.04,1.366)	1.185 * (1.029,1.365)	1.177 * (1.024,1.354)
Weight Gain 3+ Units	2.021 *** (1.634,2.499)	2.064 *** (1.666,2.558)	1.972 *** (1.58,2.462)	1.822 *** (1.46,2.273)
Underweight	2.889 *** (2.018,4.135)	2.934 *** (1.967,4.378)	2.452 *** (1.598,3.765)	2.252 *** (1.491,3.403)
Overweight	0.95 . (0.848,1.064)	0.84 (0.707,0.985)	0.901 . (0.797,1.017)	0.908 . (0.804,1.025)
Obese I	0.938 . (0.814,1.082)	0.861 (0.715,0.997)	1.271 . (1.034,1.53)	1.115 . (0.985,1.362)
Obese II/III	1.3 ** (1.09,1.551)	1.236 * (1.032,1.482)	1.519 *** (1.26,1.832)	1.974 * (1.655,2.238)

Notes:

Model 1: Includes only baseline weight status and time-dependent weight change.

Model 2: Adds SES and socio-demographic covariates (both baseline and time-varying).

Model 3: Adds confounding by time-dependent health behaviors.

Model 4: Adds confounding by time-dependent health conditions.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Diagram A1: Simplified Causal Associations between Weight Change and Mortality

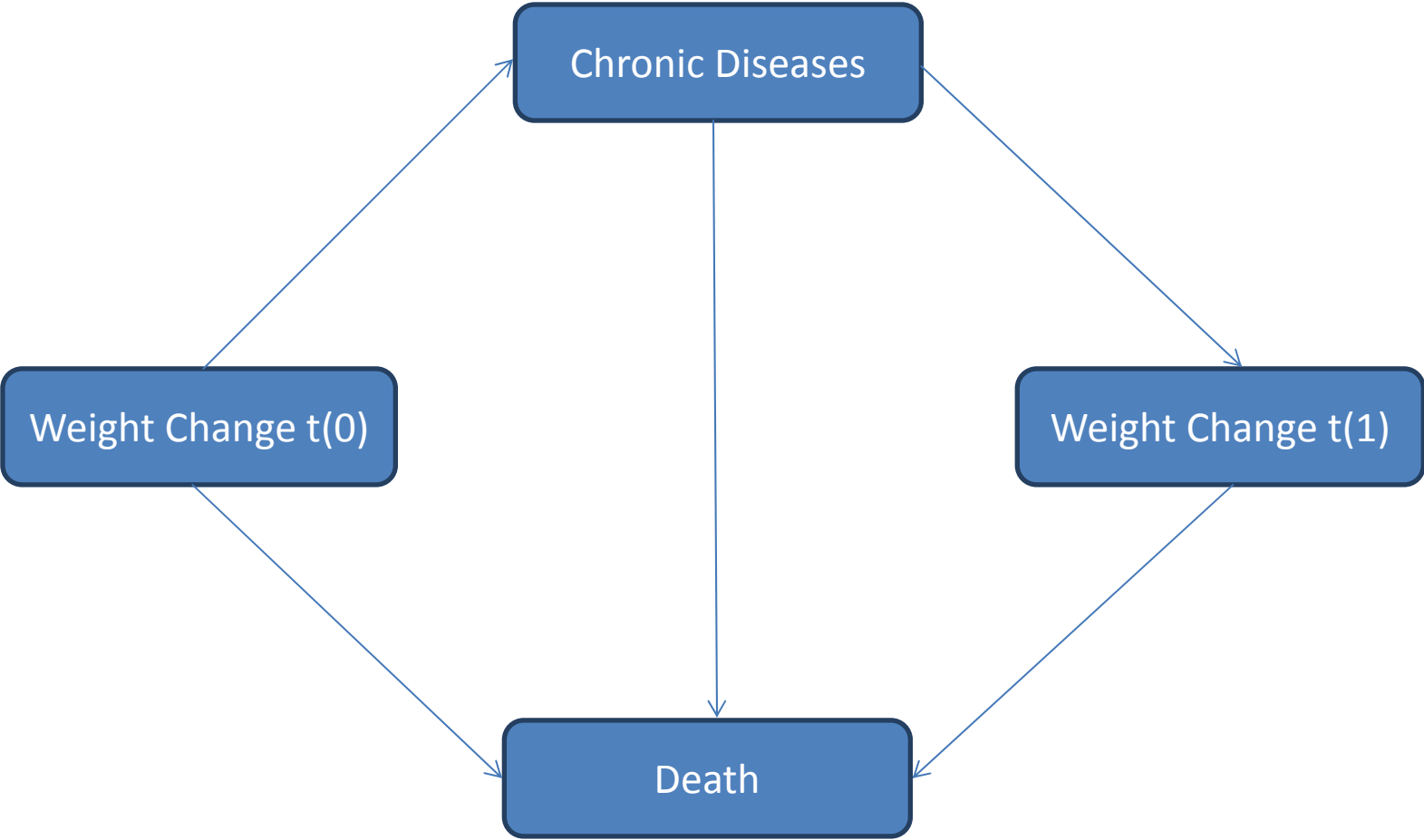
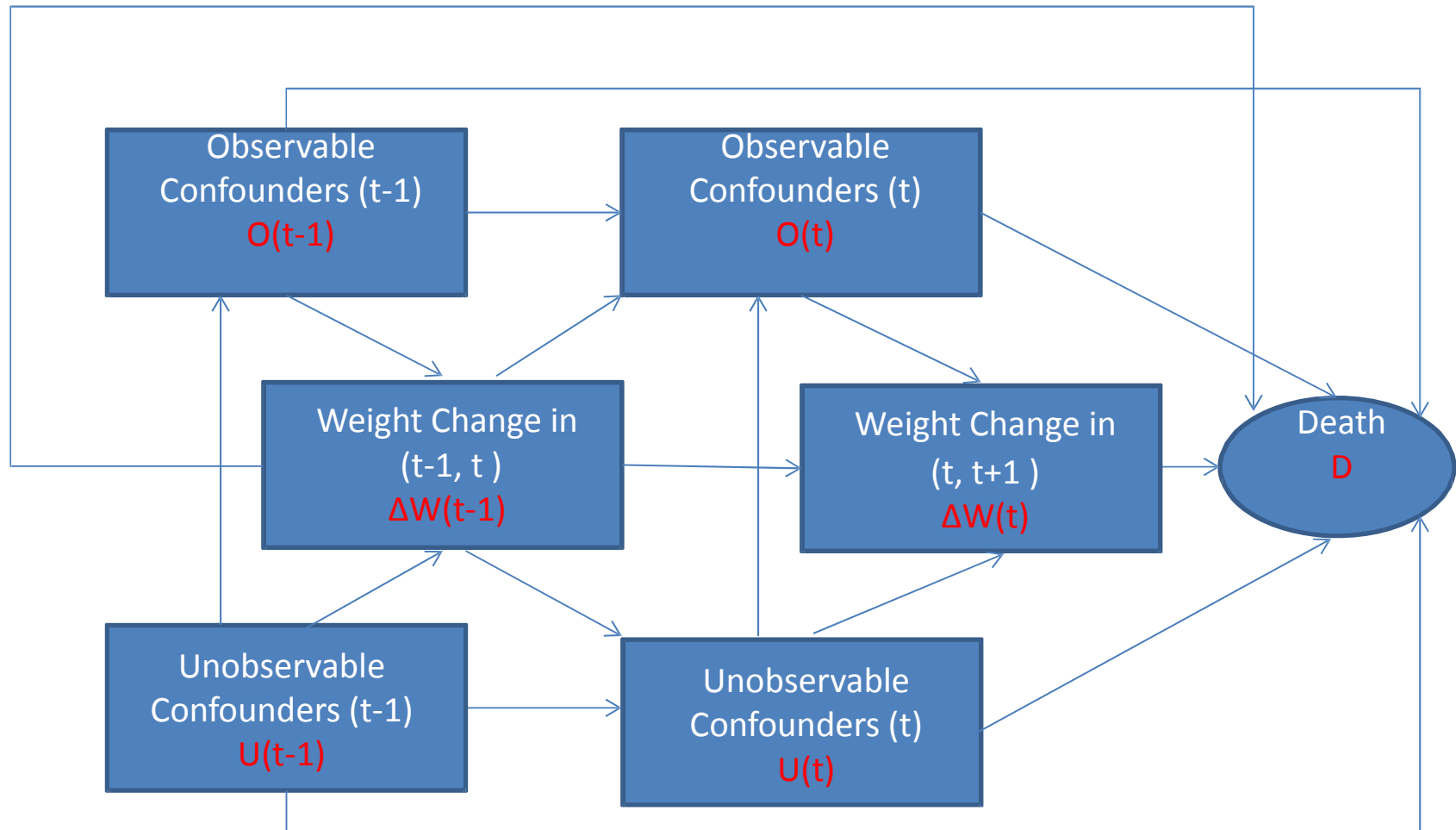


Diagram A2: Comprehensive Causal Associations between Weight Change and Mortality



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