# Body Mass Index (BMI) Change and All-Cause Mortality in the Middle-aged and Older Population

By

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Submitted to the
University of Hawaiʻi at Mānoa
Office of Public Health Studies
In partial fulfillment of the Requirements for the
Master of Science Degree
in Epidemiology

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May 2017

## ACKNOWLEDGMENTS

I appreciate my advisor, Yan Yan Wu, for her patient and professional support and guidance during all stages of this thesis and my Master's program. I would also like to thank the members of my committee, Andrew Grandinetti and Eric Hurwitz, for their helpful suggestions and comments.

I would also like to extend my gratitude to Alan Katz, Xiaoxin Ivy Mu, and Ronald Heck, for their patient, thoughtful guidance, and support. Thanks to all the faculties in Health and Retirement Study for providing the dataset.

I wish to express my appreciation to all the individuals who join in this project. And thank you to all the people who supported me to stay focused on this project and encouraged me when I met problems.

**ABSTRACT**

***Objectives*** (i) To investigate the BMI change distribution among middle-aged and older adults; (ii) to assess the magnitudes of the effect of BMI change on all-cause mortality; (iii) to examine the effect modification of the BMI change-mortality associations by gender and ethnicity among the middle-aged and older population.

***Design*** This study utilizes a nationally representative dataset from the U.S. Health and Retirement Study (HRS). The HRS is an on-going biennial longitudinal survey began in 1992 and the survey is based on a multi-stage area probability design involving geographical stratification and clustering.

***Participants*** There are a total of 24,984 participants (13,887 females and 11,097 males) aged 60 years or older with an average age of 75.68 after excluding participants without clear responses.

***Main exposures*** BMI change.

***Main outcomes*** Survival time and mortality.

***Results*** The BMI change of our study sample is normally distributed, in which most participants cluster in the stable group and fewer participants are distributed in the severe loss and gain groups. Compared with participants with stable BMI, participants with severe BMI loss, severe BMI gain, and moderate BMI gain have greater risk of mortality, the hazard ratios (HRs) and 95% confidence intervals (CIs) are: 1.13 (1.06, 1.19); 1.11 (1.03, 1.20), and 1.15 (1.06, 1.24), respectively. For females, severe BMI loss, moderate BMI gain, and severe BMI gain are associated with increased mortality (Severe loss: 1.14 (1.06, 1.23); Moderate loss: 1.02 (0.94, 1.11); Moderate gain: 1.17 (1.05, 1.29); Severe gain: 1.19 (1.08, 1.32)). The association is weaker for males (Severe loss: 1.09 (1.00, 1.19); Moderate loss: 1.02 (0.94, 1.11); Moderate gain: 1.06 (0.95, 1.18); Severe gain: 1.12 (0.99, 1.27)).

***Conclusion*** Severe BMI loss, severe BMI gain, and moderate BMI gain are associated with increased all-cause mortality among the middle-aged and older population in the United States, but moderate BMI loss is not a risk factor for mortality. The results of subgroup analysis suggest gender and racial differences in the association between BMI change and all-cause mortality. These results of subgroup analysis indicate that females are more sensitive than males, and Caucasians are more sensitive than African Americans. Public health efforts should encourage weight control among the middle-aged and older population.

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# CHAPTER I. INTRODUCTION

## *1.1 Body Mass Index (BMI) and mortality*

Body Mass Index (BMI), a standard tool for measuring the human body by weight and height, has been used by the World Health Organization (WHO) since the early 1980s. According to the WHO, BMI (kg/m2) between 18.5 and 24.9 is regarded as a healthy range for adults on the basis of decreased mortality risk (1). However, this healthy range is predominantly based on research and studies in the early adulthood and more and more evidence showing the WHO cut-offs of BMI may not be suitable for older age groups (2).

Three major types of the association between BMI and mortality among the middle-aged and older populations are described by epidemiological research and studies——U- or J-shaped relations (3-5), an inverse association (6-12) or no significant association (13-17).

A U-shaped association between BMI and all-cause mortality was illustrated in a meta-analysis in 2014 of 32 cohort studies including 197,940 community-dwelling individuals aged >= 65 years old with the average follow-up of 12 years (18). The BMI range between 24.0 and 30.9 is associated with reduced mortality compared to the BMI of 23.0-23.9 (18). The lowest point of the curve for BMI and mortality is between 27.0 and 27.9 (HR: 0.90; 95% CI:0.88, 0.92) (18). The BMI ranges of 20.0-21.9 and 33.0-33.9 are both related to increased mortality [BMI of 21.0– 21.9; HR (95% CI): 1.12 (1.10, 1.13); BMI of 20.0–20.9; HR (95% CI): 1.19 (1.17, 1.22); BMI of 33.0–33.9; HR (95% CI): 1.08 (1.00, 1.15)] (18). This association remains after adjusting for demographic characteristics, pre-existing diseases, smoking status, early death and geographical location (18). Likewise, Kvamme et al. (2012) also indicated the U-shaped relation between BMI and mortality by a longitudinal cohort study following 16,711 individuals over 65 years old for 9.3 years (19). They found, for men and women, the lowest points of the curve for

BMI and mortality are the BMI ranges of 25.0-27.4 and 25.0-32.4 respectively (19). However, a recent prospective longitudinal study indicated the age, sex and smoking history could modify the association between BMI and mortality. The study involving 1,231,829 Koreans aged between 30 and 95 years old also shows the U-shaped relations, but the association of BMI and mortality varied with the cause of death and was modified by age, sex and smoking history (20). The discrepancy can be explained by the effect of different ethnicity on BMI range (21).

The inverse relation is supported by several studies (22-23). One is an American longitudinal study in 2008 using the data from National Long Term Care Survey, which followed 4791 individuals aged greater than or equal to 65 years for 9 years (22). They find for both genders the lower BMI is associated with increased death rate, even after adjusting for age, race, alcohol, smoking, and some chronic diseases. [for men: BMI of <18.5:HR=2.24 (1.74, 2.88); BMI of 18.5-21.9: HR=1.51(1.26, 1.80); BMI of 25-29.9: HR=0.80 (0.68, 0.93); For women: BMI of <18.5: HR= 1.70 (1.44, 2.02); BMI of 18.5-21.9: HR=1.15 (1.00, 1.31), BMI of 25.0-29.9: HR= 0.84 (0.73, 0.95), BMI of 30.0-34.9: HR= 0.75 (0.62, 0.89); The reference group is BMI of 22.0-24.9] (22). Another cohort study involving 9240 Australians aged between 70 and 75 years old also indicates an inverse association between BMI level and mortality that compared to the normal BMI range (18.5-24.9), underweight (BMI <18.5) individuals have raised death rate [HR=1.76 (1.39, 2.22)] and overweight (BMI of 25.0-29.9) is associated with lower mortality [HR= 0.87 (0.78, 0.94] (23). However, most research and studies only focus on the Caucasians, so the inverse association between BMI and mortality may not be generalizable to other ethnic groups.

Some evidence shows that BMI varies according to ethnicity, education level, and smoking (24-30), but many studies of the relationship between BMI and mortality among the middle-aged and older populations did not adjust for all of those potential confounders (31).

### *1.2 Weight or BMI change and mortality*

In the past two decades, the weight of the adolescent and adult populations in the United States has been rising and more than half of the populations in many other developed countries are overweight and obese (32-33). It is well established that excess body mass in young adulthood is associated with a high incidence rate of chronic diseases (34-35) and increased mortality (36-38). However, the association between weight or BMI change and mortality has not been described well in the middle-aged and older adults (39). Many studies compared the associations of weight or body mass and mortality in two (19, 40-44) or more different age groups (45-46) and discovered that BMI associated with minimal mortality increases with age (47).

#### *1.2.1 Weight loss and mortality*

Weight loss is frequently observed among the frailest older people (48). Besides, weight loss is often a sign for severe diseases (49). Several previous studies and reviews indicated a significant association between the weight loss and increased mortality (50-56). A recent meta-analysis combining 17 prospective cohort studies in Western countries and Asian countries indicates that the higher all-cause mortality is associated with weight loss [RR= 1.67; 95% CI: (1.51–1.85)] (18). Another large-scale case-control study, focusing on Europeans aged over 65 years old, also has a similar conclusion that the individuals who lose more than 1 kg/year have 1.65 times higher risk of mortality than those who have stable weights (57). However, there is some evidence showing the association between weight loss and higher mortality varies by gender and initial weight or BMI. A multi-ethnic national cohort study among US men and women suggests that weight loss of 15% or more of initial weight is related to increased mortality only among overweight males and females regardless of initial BMI (58). Another study utilizing national representative dataset suggests that weight loss is related to excess mortality only for those initial BMI level < 32 kg/m$^2$, and the larger losses and lower initial BMI, the higher excess risk (59). Except for gender and initial BMI, dieting and physical exercise also may modify weight. Some observational studies have shown that both intentional and unintentional weight losses may be related to increased mortality (60-61).

However, a contrary opinion that weight loss is not significantly associated with higher mortality is supported by a European prospective study, which followed 1,053 individuals aged between 70 and 77 years old for 6 years. It suggests that both small weight loss (lost 1.0 to 3.2 kg/year) and large weight loss (lost >3.2 kg/year) are not related to increased mortality (42). Likewise, Murphy et al., who conducted a cohort study among US people aged between 70 and 79 years old in 2014, illustrate that for both genders, the individuals who lost > 5% of initial weight do not experience excess risk, comparing to those with stable weights (43).

*1.2.2 Weight gain and mortality*

Current literature seems to show a tendency that the mortality risk related to weight gain diminished as the length of follow-up decreased (57). An epidemiological study following 882 participants in Sweden for 18 years suggests that people who gained > 5% of their initial weight have 1.53 [95% CI:1.18-1.99] times higher risk of death than those with stable weights, after adjusting age, sex, education, multi-morbidity, and BMI (64). However, another prospective study with the same target population and geographic location followed 2405 people for 10 years, showing there is no relationship between weight gain (gained > 5% of initial weight) and higher death risk for both genders (65). For mild weight gain, most epidemiological studies and research seem to suggest no effect on all-cause mortality among the middle-aged and older population (57).

Studies of weight or BMI change and mortality among the middle-aged and older populations have had some limitations. Initially, most studies completely relied on self-reported weights and heights, which may diminish the precision of the estimates. Secondly, some studies had limited information on health status. Weight change could be modified by severe illness and health status. Many chronic diseases including cardiovascular disease, high blood pressure, and glucose appear to influence weight (66). And high BMI and weight gain are associated with disability, diabetes, and hypertension among old people (67). Thirdly, few studies adjusted all of the potential confounders. Many potential confounders exist in the association between weight change and mortality. Cigarette smoking related to low body weight and high mortality may distort the association (68). Gender, race, and education level are also considered as potential confounders (21).

# CHAPTER II. OBJECTIVES

In this research, we examine the association between BMI change and all-cause mortality adjusting demographic characteristics, health and behavioral factors. We use the nationally representative survey data and Cox's proportional hazards regression analysis to estimate the association between BMI change and all-cause mortality among middle-aged and older adults, adjusting for demographic factors, initial BMI, health and behavioral factors.

The aims of this research are (i) to investigate the BMI change distribution among middle-aged and older adults; (ii) to assess the magnitudes of the effect of BMI change on mortality; and (iii) to examine the effect modification of the BMI change-mortality associations by gender and ethnicity among the middle-aged and older population.

# CHAPTER III. METHODS

## *3.1 Data source*

Our data are derived from Health and Retirement Study (HRS), which is a multi-ethnic United States representative longitudinal survey with a sample size of about 37,000 participants and more than 20 years of follow-up. The survey was established in 1992 and the follow-up investigations were conducted every two years, to provide a national and longitudinal resource for data on the health and economic change associated with aging at both individual and population level.

The HRS utilizes a multi-stage area probability sample design, comprising geographically stratified and cluster sampling and oversampling of African-American and Hispanic households. Each sampled household unit is required to have a brief household screening to determine eligibility. The age and marital/patterned status of adults (age >18) in households are investigated. The primary respondents are determined by random selection from all eligible household members who are 50 years of age or older. If the selected respondent is coupled, their spouse or partner is also included in the sample. HRS also oversampled Hispanic and African-American groups at approximately twice the rate of the Caucasians to avoid the low response rate.

HRS baseline interviews were mainly conducted by face-to-face (FTF). For the follow-up interviews, the primary mode was by telephone before 2004 and since 2006 HRS adopted a mixed-mode design that half of the sample was interviewed by telephone and other half was assigned an FTF interview with physical and biological measures and a psychosocial questionnaire. Core interviews and mail surveys are conducted by English and Spanish.

The participants in our research are from HRS, which has 6 entry cohorts. Our study sample is from the initial HRS cohort, the Children of Depression cohort (CODA, born 1924–30), Mid Baby Boomers cohort (MBB, born 1954–59), and the War Babies cohort (WB, born 1942–47). We excluded Assets and Health Dynamics Among the Oldest Old cohort (AHEAD) and Early Baby Boomers cohort (EBB), because of lack of weight change measurement and inconsistent questionnaire with other cohorts respectively. Only those who were 60 years of age or older at baseline are included in the analysis.

### *3.2 Variables*

The dependent variables are survival time and mortality. We choose age as survival time. The vital status is obtained from the interviews and the National Death Index (NDI). For the individuals without vital records in NDI and interviews, death time is estimated between the interview where the person was last seen alive and the next interview.

The independent variable is BMI change. We classified all participants into five BMI change groups on the basis of the most recent BMI change; please see BMI change classification for detail. Initial BMI (weight (kg)/height ($m^2$)) is calculated by the measured weight and height, which is treated as continuous variable. For deceased participants, BMI two years prior to death is regarded as initial BMI. For living participants, BMI of the second most recent interview is regarded as initial BMI.

Health status and chronic disease conditions are both self-reported. Health status is reported as excellent, very good, good, fair, and poor. The chronic disease conditions in HRS are ensured by two types of questions. One is asked in the first interview that “Has a doctor ever told you that you have …” and another question is asked in the second interview that “Since we last talked to you, has a doctor told you that you have …”. If the participant answered affirmatively in the first interview but denied in the second interview, then he or she is regarded as not having this condition for both interviews. The chronic disease conditions include hypertension, diabetes mellitus, cancer, heart problem, and stroke. Additional target disease-related information is also investigated when the participant reports a chronic disease condition (69).

Two measures of physical function are also considered. The activities of daily living (ADL) is the measurement of physical disability, including six daily activities: eating, bathing, dressing, toileting, transferring (walking) and continence. Mobility impairment is measured by the completion of five tasks including walking several blocks, walking one block, walking across the room, climbing several flights of stairs and climbing one flight of stairs.

Additional control variables are sex, age, race, education level, and smoking status.

Variables controlled in the survival analysis are treated as potential confounders. There are two reasons. First, the variables chosen as potential confounders are based on literature reviews. Secondly, the controlled variables in our study have the properties of confounders that controlled variables are associated with outcome variable and exposure variable, but not intermediates in the causal pathway between exposure and outcome.

### *3.3 Statistical methods*

#### *3.3.1 Descriptive analysis*

In the descriptive analysis, we described and compared the demographic characteristics (sex, age, race, and education level), health-related features (self-reported health status, mobility impairment score, ADL score, and smoking status), and chronic disease conditions between each BMI change group. All continuous variables were reported as means ± standard deviation and categorical variables were reported as percentages. Differences in the continuous variables between groups were assessed by t-tests and categorical variables are compared using the chi-square test.

### *3.3.2 Aim 1. BMI change classification*

In this study, BMI is measured repeatedly over time for each participant, so there are a large number of BMI values in the dataset. In order to organize the BMI values so that it can be understood more easily and the information retrieved more efficiently, I summarized and classified the data into small number of groups based on each participant's BMI change during the recent two years. For deceased participants, the two-year BMI change before death is regarded as the most recent BMI change. For living participants, BMI change between the most recent two interviews is regarded as the most recent BMI change. Clinically significant weight loss is defined as a loss of 4.5kg or > 5% of initial body weight during 6-12 months (70). Losing >10% of initial body weight is regarded as protein-energy malnutrition, which is considered to represent severe weight loss (70). So we choose 5% and 10% as the cut-offs of BMI change. Therefore, BMI change was classified into five groups. Stable group was defined as BMI change within 5% of initial BMI, moderate BMI loss and moderate BMI gain are defined as lose 5%-10% of initial BMI and gain 5%-10% of initial BMI respectively, severe BMI loss and severe BMI gain are defined as lose more than 10% of initial BMI and gain more than 10% of initial BMI respectively.

### *3.3.3 Aim 2 and 3. Cox's proportional hazards regression analysis*

Cox proportional hazard regression analysis is used to estimate hazard ratios (HR) and 95% confidence intervals (CI) of mortality and survival time in each BMI change group, choosing the group of participants with stable BMI as the reference. We utilize five proportional hazard models to estimate the BMI change on mortality. The model equations are shown as follows:

Crude Model: $h(t;x) = h(t) \exp(\beta_1 \text{BMI change})$

Model 1: $h(t;x) = h(t) \exp(\beta_1 \text{BMI change} + \beta_2 \text{ initial BMI})$

Model 2: $h(t;x) = h(t) \exp(\beta_1 \text{BMI change} + \beta_2 \text{ initial BMI} + \beta_3 \text{ demographic characteristics})$

Model 3: $h(t;x) = h(t) \exp(\beta_1 \text{BMI change} + \beta_2 \text{ initial BMI} + \beta_3 \text{ demographic characteristics} + \beta_4 \text{ health-related features})$

Model 4: $h(t;x) = h(t) \exp(\beta_1 \text{BMI change} + \beta_2 \text{ initial BMI} + \beta_3 \text{ demographic characteristics} + \beta_4 \text{ health-related features} + \beta_5 \text{ chronic diseases})$

Model 1 estimates the main effect of initial BMI and BMI change. Model 2 assesses the main effect by adjusting demographic characteristics. Model 3 extends Model 2 by adjusting health-related features. Model 4 is our final model which adjusts for chronic diseases on the basis of Model 3.

To assess the effect-measure modification of BMI change and all-cause mortality with gender and race, subgroup analyses by gender and race (Caucasian, Hispanic, and African American) are conducted.

All analyses were performed using R 3.2.3.

# CHAPTER IV. RESULTS

Of 25,784 participants, 800 individuals do not have clear responses on age, gender, race, smoking status, BMI, education level, marital status, self-reported health condition, and chronic conditions. Therefore, a total of 24,984 individuals have valid data—that is, completed questionnaire, physical measurements, and a written informed consent form (See details in Chart 1).

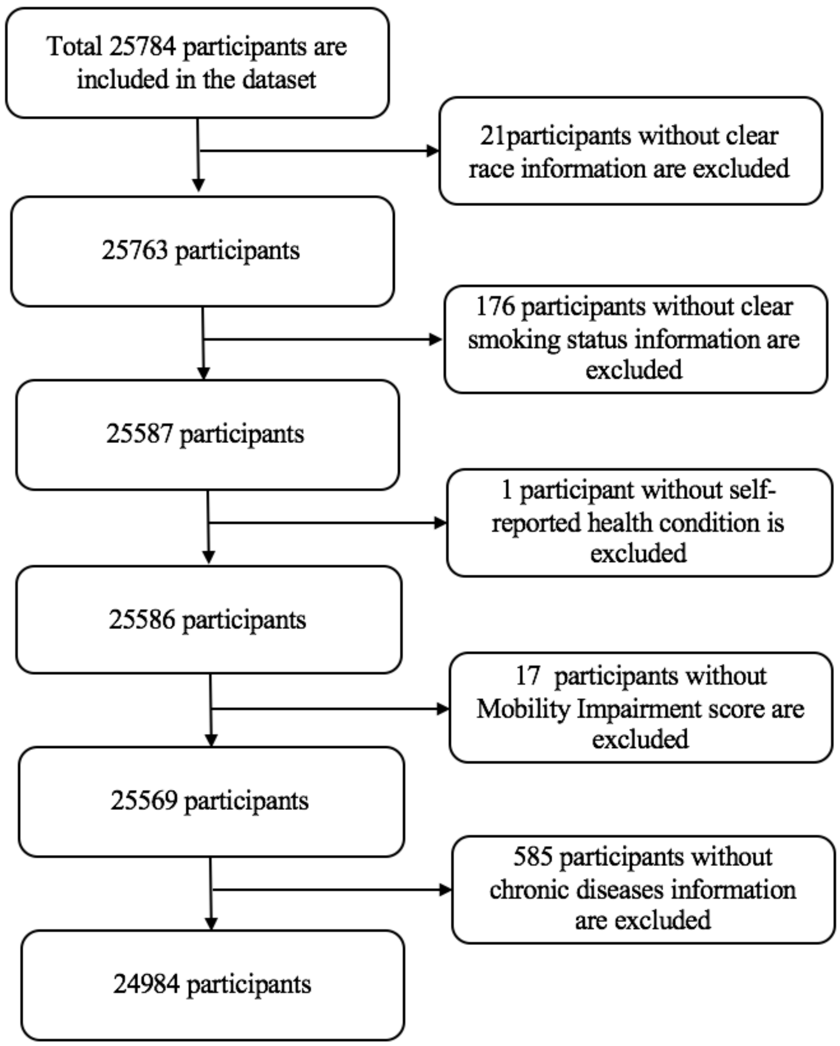



**Chart 1. Participants inclusion flow**

### *4.1 Descriptive Analysis*

Table 1 shows demographic characteristics, health-related characteristics, and mortality of the study population.

Our study population consists of 24,984 participants with an average age of 75.68 years old; 55.58% female and 44.42% male. Most participants are Caucasian (79.77%), African Americans make up to 15.49%, and only 2.55% of participants are Hispanic. There are 28.35% of individuals without any degree, 46.10% of participants with high school degree or below, and 21.27% of participants with bachelors or higher degree. In total, 13031 (52.16%) are married and 11953 (47.84%) participants are not married.

The average BMI of the study population is 27.19 with a standard deviation of 5.79. According to their BMI change during follow-up, participants are divided into five BMI change groups. Of all participants, 14,067 (56.30%) participants have stable BMI during the follow-up, 3490 (13.97%) participants losing 5% to 10% of BMI during the follow-up are assigned to moderate BMI loss group, 3200 (12.81%) individuals losing more than 10% of BMI are assigned to severe BMI loss group, 2464 (9.86%) participants gaining 5% to 10% of BMI are marked as moderate BMI gain group, and 1763 (7.06%) individuals gaining more than 10% of BMI are marked as severe BMI gain group.

Most participants in the study population had smoking experience. There are 11,754 (47.05%) previous smokers, 2927 (11.72%) current smokers, and 10,303 (41.24%) non-smokers. Most participants rated their overall health as “good” or “very good”, but 17.09% of participants rated their health as poor; only 6.64% of participants rated their overall health as excellent. Mobility impairment is measured by the completion of five tasks including walking several blocks, walking one block, walking across the room, climbing several flights of stairs and

**TABLE 1. Baseline Demographic and Health Related Characteristics in the Whole Sample**

| Variable | Total (n=24984) | Alive (n=15738) | Deceased (n=9246) | p value |
|---|---|---|---|---|
| **Age; Mean (SD)** | 75.68 (9.95) | 72.84 (8.91) | 80.52 (9.76) | < .0001 |
| **Gender; n (%)** | | | | < .0001 |
| Female | 13887 (55.58) | 9082 (65.40) | 4805 (34.60) | |
| Male | 11097 (44.42) | 6656 (59.98) | 4441 (40.02) | |
| **Race; n (%)** | | | | < .0001 |
| Black/African American | 3871 (15.49) | 2465 (63.68) | 1406 (36.32) | |
| White/ Caucasian | 19929 (79.77) | 12357 (62.01) | 7572 (37.99) | |
| Hispanic | 637 (2.55) | 516 (81.00) | 121 (19.00) | |
| Other | 547 (2.19) | 400 (73.13) | 147 (26.87) | |
| **Education level; n (%)** | | | | < .0001 |
| No degree | 7083 (28.35) | 3371 (47.59) | 3712 (52.41) | |
| HS or below high school degree | 11517 (46.10) | 7618 (66.15) | 3899 (33.85) | |
| Bachelor's degree and higher | 5288 (21.27) | 4013 (75.89) | 1275 (24.11) | |
| Other | 1096 (4.39) | 736 (67.15) | 360 (32.85) | |
| **Marital Status; n (%)** | | | | < .0001 |
| Married | 13031 (52.16) | 8860 (67.99) | 4171 (32.01) | |
| Unmarried | 11953 (47.84) | 6878 (57.54) | 5075 (42.46) | |
| **BMI; Mean (SD)** | 27.19 (5.79) | 27.99 (5.77) | 25.83 (5.57) | < .0001 |
| **BMI change; n (%)** | | | | < .0001 |
| Severe loss | 3200 (12.81) | 1378 (43.06) | 1822 (56.94) | |
| Moderate loss | 3490 (13.97) | 1986 (56.91) | 1504 (43.09) | |
| Stable | 14067 (56.30) | 9724 (69.13) | 4343 (30.87) | |
| Moderate gain | 2464 (9.86) | 1655 (67.17) | 809 (32.83) | |
| Severe gain | 1763 (7.06) | 995 (56.44) | 768 (43.56) | |
| **Smoking status; n (%)** | | | | < .0001 |
| non-smoker | 10303 (41.24) | 6952 (67.48) | 3351 (32.52) | |
| previous smoker | 11754 (47.05) | 7110 (60.49) | 4644 (39.51) | |
| current smoker | 2927 (11.72) | 1676 (57.26) | 1251 (42.74) | |
| **Health condition; n (%)** | | | | < .0001 |
| Excellent | 1658 (6.64) | 1308 (78.89) | 350 (21.11) | |
| very good | 5643 (22.59) | 4534 (80.35) | 1109 (19.65) | |
| good | 7265 (29.08) | 5040 (69.37) | 2225 (30.63) | |
| fair | 6149 (24.61) | 3373 (54.85) | 2776 (45.15) | |
| poor | 4269 (17.09) | 1483 (34.74) | 2786 (65.26) | |
| **mobility impairment score; mean(SD)** | 1.78 (1.80) | 1.37 (1.63) | 2.48 (1.88) | < .0001 |

| (Continued) TABLE 1. Baseline Demographic and Health Related Characteristics in the Whole Sample | | | | |
|---|---|---|---|---|
| **Variable** | **Total (n=24984)** | **Alive (n=15738)** | **Deceased (n=9246)** | **p value** |
| **ADL score; mean(SD)** | 0.82 (1.49) | 0.48 (1.14) | 1.41 (1.80) | < .0001 |
| **Diabetes; n (%)** | 6381 (25.54) | 3942 (25.05) | 2439 (26.38) | 0.0206 |
| **High blood pressure; n (%)** | 16197 (64.83) | 10389 (66.01) | 5808 (62.82) | < .0001 |
| **Cancer; n (%)** | 5117 (20.48) | 2839 (18.04) | 2278 (24.64) | < .0001 |
| **Stroke; n (%)** | 3191 (12.77) | 1484 (9.43) | 1707 (18.46) | < .0001 |
| **Heart problem; n (%)** | 8691 (34.79) | 4616 (29.33) | 4075 (44.07) | < .0001 |

climbing one flight of stairs. The higher score, the more mobility impairment. The average mobility impairment score is 1.78, which means most participants can finish more than three tasks in the mobility impairment test if it is regarded as a normal distribution. The activities of daily living (ADL) is the measurement of physical disability, including six daily activities: eating, bathing, dressing, toileting, transferring (walking) and continence. The higher score, the more difficult to do daily activities. The average Activities of Daily Living score is 0.82 with a standard deviation of 1.49, which means most participants can finish five daily activities in the test if it is regarded as a normal distribution, but the ADL with a relatively large standard deviation, which means the ADL scores in the study population are farther away from the average score. For the chronic diseases, there are 6381 (25.54%) participants with diabetes, 16197 (64.83%) individuals with high blood pressure, 5117 (20.48%) individuals with cancer, 3191 (12.77%) participants with stroke, and 8691 (34.79%) participants with heart problems.

In the total study population, 9246 participants died during follow-up (crude mortality = 37.01%). Compared with the living participants, deceased participants are older and with lower BMI. Female participants have a lower crude mortality than males (Female crude mortality: 34.60%; Male crude mortality: 40.02%).

**TABLE 2. Baseline Demographic and Health Related Characteristics in the Whole Sample and Within Weight Change Categories**

| Variable | Total (n=24984) | BMI change group: Severe Loss (n=3783) | Moderate Loss (n=4356) | Stable (n=18675) | Moderate Gain (n=3411) | Severe Gain (n=2365) | p value |
|---|---|---|---|---|---|---|---|
| **Age; Mean (SD)** | 75.68 (9.95) | 78.60 (10.18) | 76.94 (10.08) | 74.80 (9.61) | 74.42 (9.93) | 76.72 (10.54) | <.0001 |
| **Gender; n (%)** | | | | | | | <.0001 |
| Female | 13887 (55.58) | 1926 (13.87) | 1941 (13.98) | 7458 (53.70) | 1396 (10.05) | 1166 (8.40) | |
| Male | 11097 (44.42) | 1274 (11.48) | 1549 (13.96) | 6609 (59.56) | 1068 (9.62) | 587 (5.38) | |
| **Race; n (%)** | | | | | | | <.0001 |
| Black/African American | 3871 (15.49) | 596 (15.40) | 578 (14.93) | 1997 (51.59) | 375 (9.69) | 325 (8.40) | |
| White/ Caucasian | 19929 (79.77) | 2474 (12.41) | 2740 (13.75) | 11404 (57.22) | 1956 (9.81) | 1355 (6.80) | |
| Hispanic | 637 (2.55) | 71 (11.15) | 95 (14.91) | 357 (56.04) | 66 (10.36) | 48 (7.54) | |
| Other | 547 (2.19) | 59 (10.79) | 77 (14.08) | 309 (56.49) | 67 (12.25) | 35 (6.40) | |
| **Education level; n (%)** | | | | | | | <.0001 |
| No degree | 7083 (28.35) | 1221 (17.24) | 1044 (14.74) | 3521 (49.71) | 667 (9.42) | 630 (8.89) | |
| HS or below high school degree | 11517 (46.10) | 1373 (11.92) | 1634 (14.19) | 6597 (57.28) | 1137 (9.87) | 776 (6.74) | |
| Bachelor's degree and higher | 5288 (21.27) | 470 (8.89) | 649 (12.27) | 3357 (63.48) | 543 (10.27) | 269 (5.09) | |
| Other | 1096 (4.39) | 136 (12.41) | 163 (14.87) | 592 (54.01) | 117 (10.68) | 88 (8.03) | |
| **Marital Status; n (%)** | | | | | | | <.0001 |
| Married | 13031 (52.16) | 1404 (10.77) | 1704 (13.08) | 7929 (60.85) | 1279 (9.82) | 715 (5.49) | |
| Never married | 11953 (47.84) | 1796 (15.03) | 1786 (14.94) | 6138 (51.35) | 1185 (9.91) | 1048 (8.77) | |
| **BMI; Mean (SD)** | 27.19 (5.79) | 27.92 (6.59) | 27.66 (5.93) | 27.21 (5.50) | 26.63 (5.47) | 25.51 (6.26) | <.0001 |
| **Smoking status; n (%)** | | | | | | | 0.4194 |
| non-smoker | 10303 (41.24) | 1310 (12.71) | 1414 (13.72) | 5819 (56.48) | 1027 (9.97) | 733 (7.11) | |
| previous smoker | 11754 (47.05) | 1495 (12.72) | 1630 (13.87) | 6661 (56.67) | 1145 (9.74) | 823 (7.00) | |

**(Continued) TABLE 2. Baseline Demographic and Health Related Characteristics in the Whole Sample and Within Weight Change Categories**

| Variable | Total (n=24984) | BMI change group | | | | | p value |
|---|---|---|---|---|---|---|---|
| | | Severe Loss (n=3783) | Moderate Loss (n=4356) | Stable (n=18675) | Moderate Gain (n=3411) | Severe Gain (n=2365) | |
| current smoker | 2927 (11.72) | 395 (13.50) | 446 (15.34) | 1587 (54.22) | 292 (9.98) | 207 (7.07) | |
| **Health condition; n (%)** | | | | | | | <.0001 |
| Excellent | 1658 (6.64) | 121 (7.30) | 182 (10.98) | 1109 (66.89) | 175 (10.55) | 71 (4.28) | |
| very good | 5643 (22.59) | 353 (6.26) | 673 (11.93) | 3762 (66.67) | 563 (9.98) | 292 (5.17)) | |
| good | 7265 (29.08) | 715 (9.84) | 976 (13.43) | 4352 (59.90) | 752 (10.35) | 470 (6.47) | |
| fair | 6149 (24.61) | 883 (14.36) | 992 (16.13) | 3162 (51.42) | 587 (9.54) | 525 (8.54) | |
| poor | 4269 (17.09) | 1128 (26.42) | 667 (15.62) | 1682 (39.40) | 387 (9.07) | 405 (9.49) | |
| **mobility impairment score; mean(SD)** | 1.78 (1.80) | 2.64 (1.89) | 1.99 (1.81) | 1.46 (1.68) | 1.76 (1.77) | 2.38 (1.88) | <.0001 |
| **ADL score; mean(SD)** | 0.82 (1.49) | 1.61 (1.91) | 0.88 (1.50) | 0.57 (1.25) | 0.77 (1.45) | 1.33 (1.78) | <.0001 |
| **Diabetes; n (%)** | 6381 (25.54) | 911 (28.45) | 958 (27.45) | 3437 (24.43) | 591 (23.99) | 484 (27.45) | <.0001 |
| **High blood pressure; n (%)** | 16197 (64.83) | 2133 (66.66) | 2324 (66.60) | 8903 (63.29) | 1632 (66.23) | 1205 (68.35) | <.0001 |
| **Cancer; n (%)** | 5117 (20.48) | 813 (25.41) | 806 (23.09) | 2700 (19.19) | 486 (19.72) | 312 (17.70) | <.0001 |
| **Stroke; n (%)** | 3191 (12.77) | 623 (19.47) | 517 (14.81) | 1461 (10.39) | 302 (12.26) | 288 (16.34) | <.0001 |
| **Heart problem; n (%)** | 8691 (34.79) | 1361 (42.53) | 1354 (38.80) | 4469 (31.77) | 885 (35.92) | 622 (35.28) | <.0001 |

Caucasian participants have the greatest crude mortality, which is 37.99%, and Hispanic participants have the lowest crude mortality, which is only 19.00%, compared with the African American people. In the aspect of education, the higher education level, the lower crude mortality rate. The crude mortality of married individuals is 32.01%, while the unmarried participants have a mortality of 42.46%. For the BMI change, the more severe BMI change, the greater crude mortality. Severe BMI loss group has the greatest crude mortality, which is 56.94%, and the crude mortality of severe BMI gain group is 43.56%. The crude mortality of moderate BMI loss is 43.09%, which is greater than the crude mortality of moderate BMI gain group (32.83%). The BMI stable group has the lowest crude mortality, which is 30.87%. Compared with the participants without any smoking experience, individuals with smoking experience have higher crude mortality, of which the crude mortalities among previous smokers and current smokers are 39.51% and 42.74%, respectively. For self-reported health status, the worse self-reported health, the higher crude mortality; however, the participants who reported their health as “Excellent” have higher crude mortality than the participants who reported their health as “very good”. This result may be caused by the small sample size of participants with “Excellent” health condition or related to the momentary recovery of consciousness just before death. For the chronic diseases, there are five chronic diseases are analyzed in our study. The deceased participants have the higher prevalence of diabetes, cancer, stroke, and heart problems, but have the lower prevalence of high blood pressure, compared with the non-deceased participants. These results can be explained by the low case-fatality rate and high prevalence of high blood pressure.

Table 2 shows demographic and health-related characteristics within BMI change groups.

The BMI change of our study sample is normally distributed, in which most participants cluster in the stable group and fewer participants are distributed in the severe loss and gain groups. The participants in the moderate gain group are youngest, and severe loss group has the oldest participants. The magnitude of BMI change among females is greater than males. The BMI changes among African Americans are larger compared to the Caucasians and Hispanic participants. Table 2 also indicates that the educational level and self-rated health are positively correlated with stable BMI. Compared with unmarried participants, married participants have more stable BMI. The BMI stable group has lower mobility impairment score and better daily self care abilities. Among the five BMI change groups, severe loss group has the highest prevalence of diabetes, cancer, stroke, and heart problems; Severe gain group has the highest prevalence of high blood pressure; Stable group has the lowest prevalence of high blood pressure, stroke, and heart problems; Moderate gain group has the lowest prevalence of diabetes; Severe gain group has the lowest prevalence of cancer.

### *4.2 Survival Analysis*

Table 3 shows the crude hazard ratios for each BMI change group and adjusted hazard ratios obtained from four multivariable models by adding (1) initial BMI, (2) demographics, (3) mobility impairment and ADL, and (4) chronic diseases sequentially.

**TABLE 3. Effect of Body Mass Index (BMI) Change on Mortality Hazard Ratio (HR) and 95% Confidence Interval (95% CI) by Model and BMI change group.**

| Model | Stable group | Severe Loss | Moderate Loss | Moderate Gain | Severe Gain |
|---|---|---|---|---|---|
| **Crude Model** | 1.00 | 1.15 (1.09, 1.22) | 1.06 (1.00, 1.12) | 1.05 (0.97, 1.13) | 1.03 (0.96, 1.11) |
| Model 1 | 1.00 | 1.13 (1.07, 1.20) | 1.05 (0.99, 1.11) | 1.08 (1.00, 1.16) | 1.08 (1.00, 1.17) |
| Model 2 | 1.00 | 1.17 (1.11, 1.24) | 1.08 (1.01, 1.14) | 1.08 (1.00, 1.16) | 1.15 (1.06, 1.24) |
| Model 3 | 1.00 | 1.11 (1.05, 1.18) | 1.02 (0.96, 1.08) | 1.11 (1.03, 1.20) | 1.15 (1.07, 1.25) |
| Model 4 | 1.00 | 1.13 (1.06, 1.19) | 1.02 (0.97, 1.09) | 1.11 (1.03, 1.20) | 1.15 (1.06, 1.24) |

**TABLE 4. Effect of Body Mass Index (BMI) Change on Mortality Hazard Ratio (HR) and 95% Confidence Interval (95% CI) by Model, Gender, and BMI change group.**

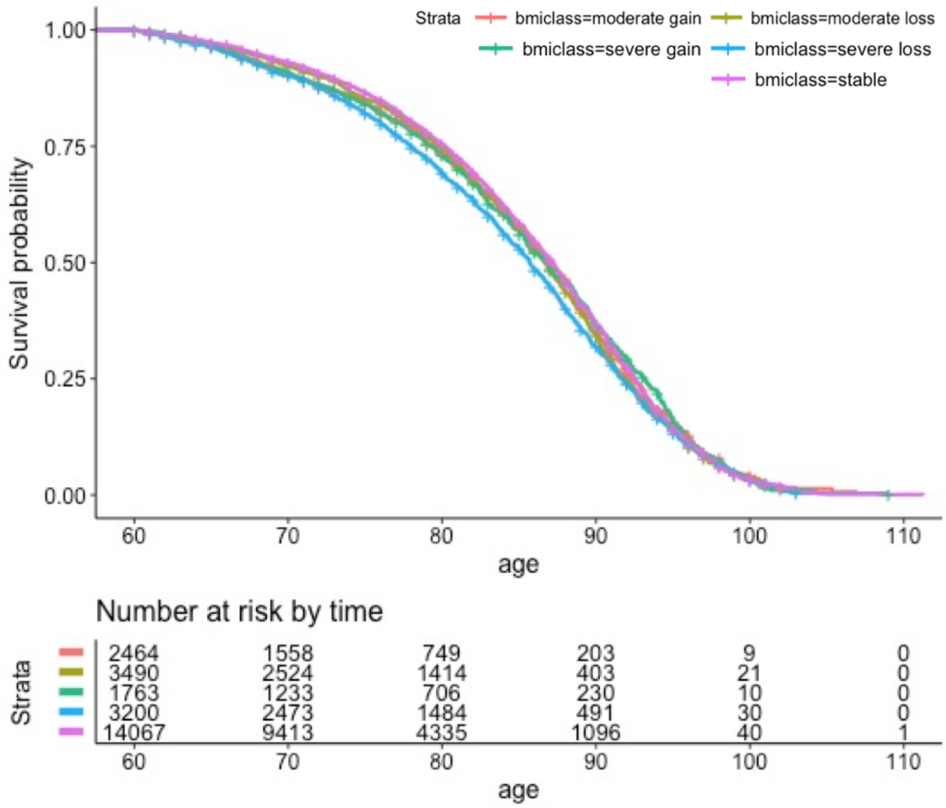
| Model | Stable group | Severe Loss | Moderate Loss | Moderate Gain | Severe Gain |
|---|---|---|---|---|---|
| **Male** | | | | | |
| Crude Model | 1.00 | 1.18 (1.09, 1.28) | 1.08 (0.99, 1.18) | 1.03 (0.93, 1.15) | 1.09 (0.96, 1.24) |
| Model 1 | 1.00 | 1.16 (1.07, 1.27) | 1.08 (0.99, 1.18) | 1.05 (0.95, 1.18) | 1.14 (1.00, 1.29) |
| Model 2 | 1.00 | 1.17 (1.08, 1.27) | 1.09 (1.00, 1.18) | 1.04 (0.94, 1.16) | 1.10 (0.97, 1.25) |
| Model 3 | 1.00 | 1.07 (0.99, 1.17) | 1.01 (0.93, 1.10) | 1.05 (0.95, 1.18) | 1.13 (1.00, 1.29) |
| Model 4 | 1.00 | 1.09 (1.00, 1.19) | 1.02 (0.94, 1.11) | 1.06 (0.95, 1.18) | 1.12 (0.99, 1.27) |
| **Female** | | | | | |
| Crude Model | 1.00 | 1.19 (1.11, 1.29) | 1.06 (0.98, 1.16) | 1.09 (0.99, 1.21) | 1.10 (1.00, 1.21) |
| Model 1 | 1.00 | 1.17 (1.08, 1.26) | 1.05 (0.97, 1.14) | 1.13 (1.01, 1.25) | 1.15 (1.04, 1.27) |
| Model 2 | 1.00 | 1.17 (1.08, 1.26) | 1.06 (0.98, 1.15) | 1.12 (1.01, 1.25) | 1.19 (1.08, 1.32) |
| Model 3 | 1.00 | 1.14 (1.05, 1.23) | 1.02 (0.94, 1.11) | 1.17 (1.06, 1.30) | 1.19 (1.08, 1.31) |
| Model 4 | 1.00 | 1.14 (1.06, 1.23) | 1.02 (0.94, 1.11) | 1.17 (1.05, 1.29) | 1.19 (1.08, 1.32) |

Crude model shows that severe BMI loss is associated with increased mortality (HR: 1.15 95% CI: 1.09, 1.22). When initial BMI is controlled in the model, from the HR changed to 1.13 (95%CI: 1.07, 1.20). Model 2 suggests severe BMI loss, moderate BMI loss, and severe BMI gain are all associated with increased mortality (Severe loss [HR (95% CI)]: 1.17 (1.11, 1.24); Moderate loss: 1.08 (1.01, 1.14); Severe gain: 1.15 (1.06, 1.24)). The results remain the same after adding mobility impairment and ADL, and chronic diseases into the model.

The survival curves are shown in the Figure 1, indicating the survival experience of each BMI change group of participants and showing the percentage surviving versus age. In the survival curves, the vertical (or Y) axis gives the survival probability, and the horizontal (or X) axis gives the age of participants. Any point on the curve gives the percentage surviving at a particular age after the start of study. It is worth noting that confounding factors are not controlled in the survival curves. From the Figure 1, we can see that the curve of severe BMI loss is continuously "below" the others, which means that the severe BMI loss is associated with a lower probability for survival and increased death rate. The curve of stable BMI is always "above" other curves, which means that stable BMI is related to higher survival probability and decreased mortality.

In summary, severe BMI loss, severe BMI gain, and moderate BMI gain are all associated with increased mortality compared with stable BMI (Severe loss: 1.13 (1.06, 1.19); Moderate gain: 1.11 (1.03, 1.20); Severe gain: 1.15 (1.06, 1.24)).

**FIGURE 1. Survival plot for weight change groups**




### *4.3 Subgroup Survival Analysis*

*4.3.1 Gender Difference*

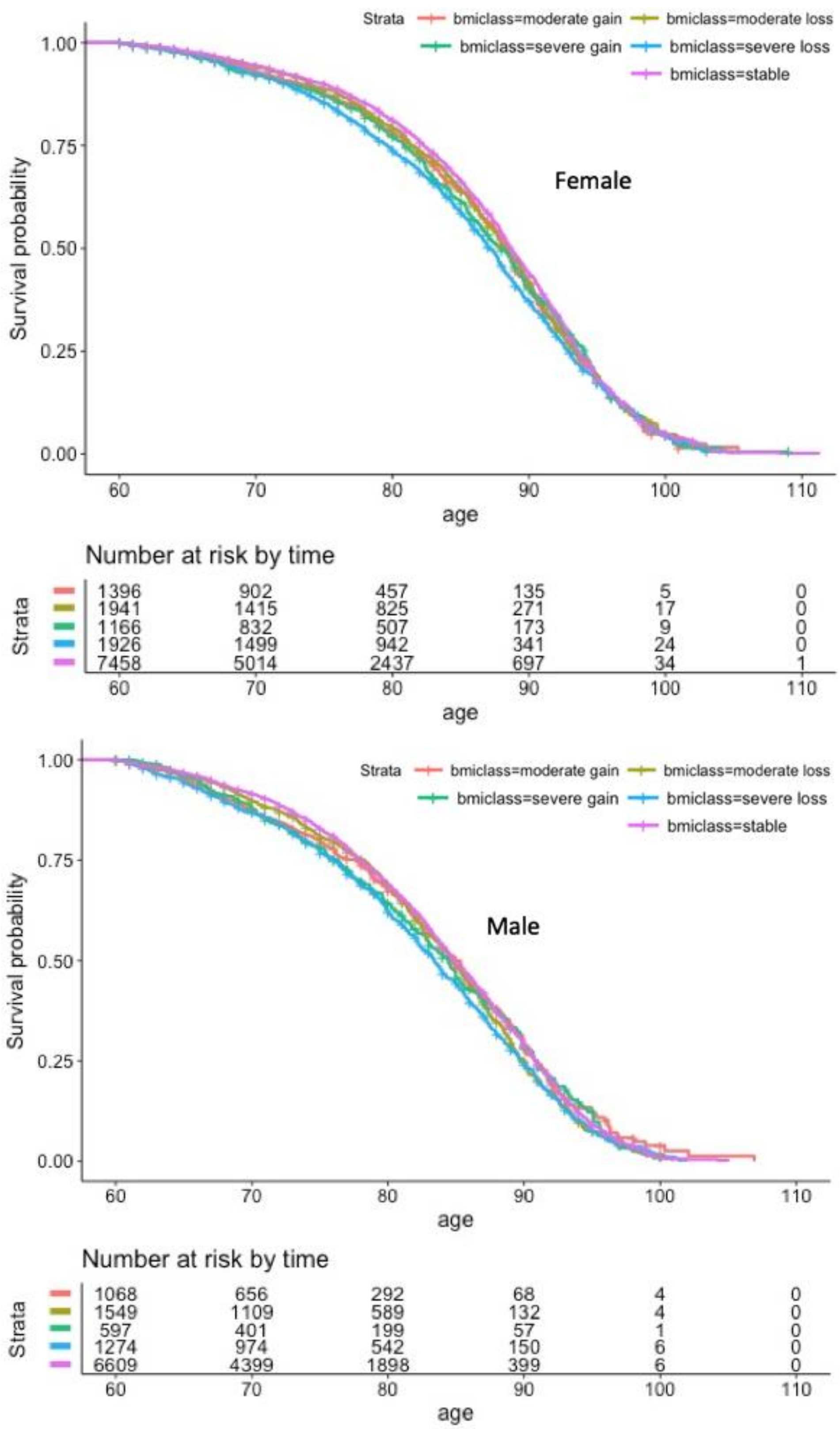
Table 4 indicates the different impacts of gender on the association between BMI change and mortality.

In males, only the association between severe BMI loss and increased mortality are significant in the crude model. However, in Model 4, where demographic characteristics, health-related features, and common chronic diseases are controlled, the BMI change also shows a trend of association  with increased mortality for males (Severe loss: 1.09 (1.00, 1.19); Moderate loss: 1.02 (0.94, 1.11); Moderate gain: 1.06 (0.95, 1.18); Severe gain: 1.12 (0.99, 1.27)). Figure 2 shows the survival curves for males, where the curves of different BMI change groups are overlapping, which match the results in Table 4.

In females, similarly after adjusting demographic characteristics, the association between severe BMI loss and increased mortality is observed in crude model, but health-related features, and common chronic diseases, the effects of BMI gain increase and effects of BMI loss decrease. In sum, for females, severe BMI loss, moderate BMI gain, and severe BMI gain are associated with increased mortality (Severe loss: 1.14 (1.06, 1.23); Moderate loss: 1.02 (0.94, 1.11); Moderate gain: 1.17 (1.05, 1.29); Severe gain: 1.19 (1.08, 1.32)). The survival curves for females are shown in Figure 2. We can see that the curves are more discrete, which means the participants in different BMI change groups have different survival trajectories.

To sum up, we observed stronger association between BMI change and increased mortality in females. Severe BMI gain, moderate BMI gain, and severe BMI loss are all connected to the higher mortality. Compare two survival plots of male and female, we can find female participants live longer than male participants in any BMI change group.

**FIGURE 2. Survival plot for weight change groups by gender**



*4.3.2 Racial difference*

Table 5 shows the different impacts of three races on the association between BMI change and mortality.

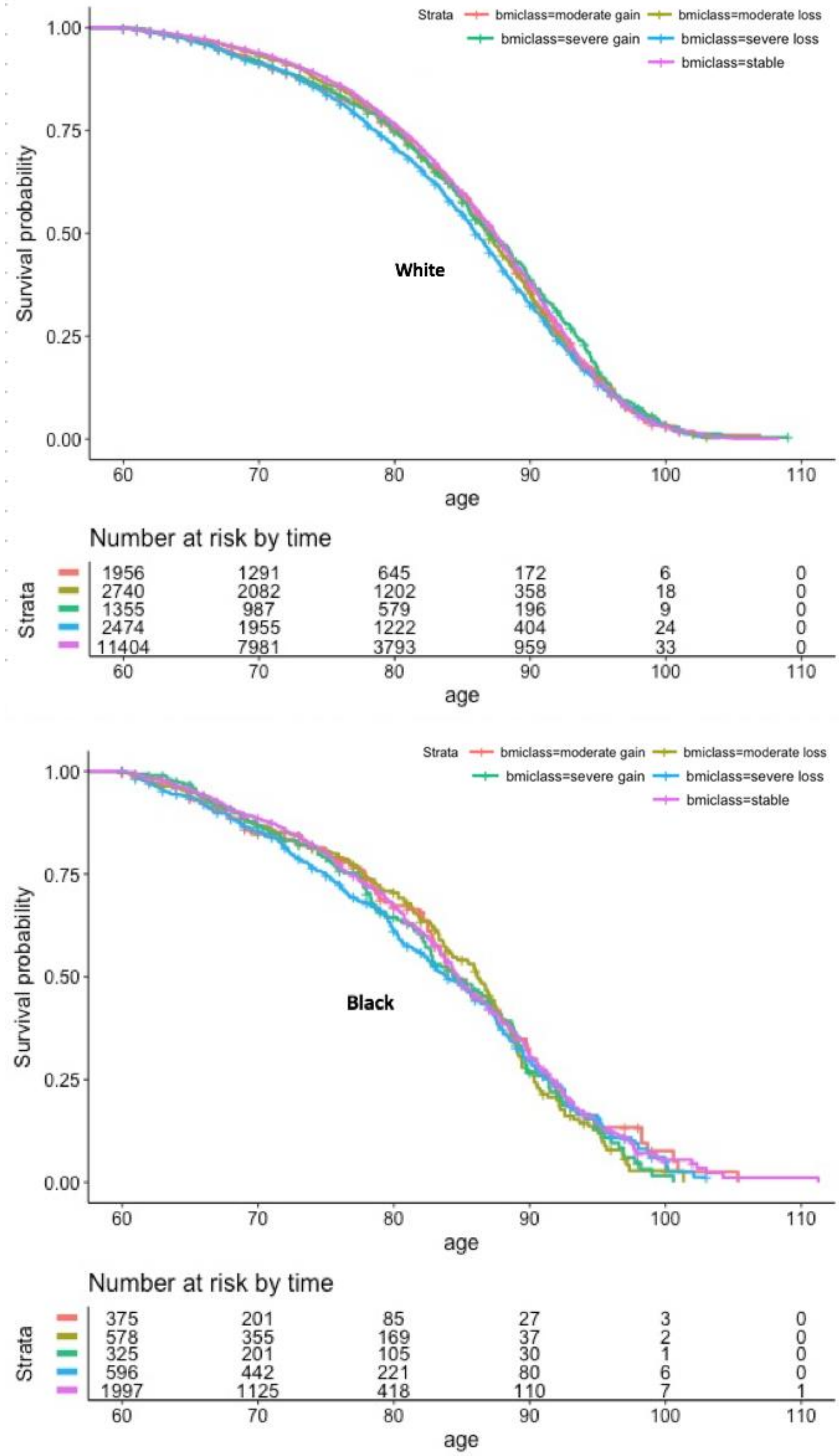
We can see in Model 4, after adjusting all the confounding factors, for Caucasian participants, severe BMI loss, moderate BMI gain, and severe BMI gain are associated with increased mortality (Severe loss: 1.13 (1.06, 1.21); Moderate loss: 11.02 (0.95, 1.09); Moderate gain: 1.14 (1.05, 1.24); Severe gain: 1.17 (1.07, 1.28)), but for African American participants, the effect of BMI change is weaker (Severe loss: 1.07 (0.93, 1.23); Moderate loss: 1.02 (0.87, 1.20); Moderate gain: 1.03 (0.84, 1.25); Severe gain: 1.09 (0.91, 1.31)), while for Hispanics, BMI severe loss has a stronger correlation with increased mortality (Severe loss: 2.09 (1.22, 3.58); Moderate loss: 1.12 (0.64, 1.95); Moderate gain: 1.85 (0.93, 3.65); Severe gain: 1.36 (0.61, 3.01)).

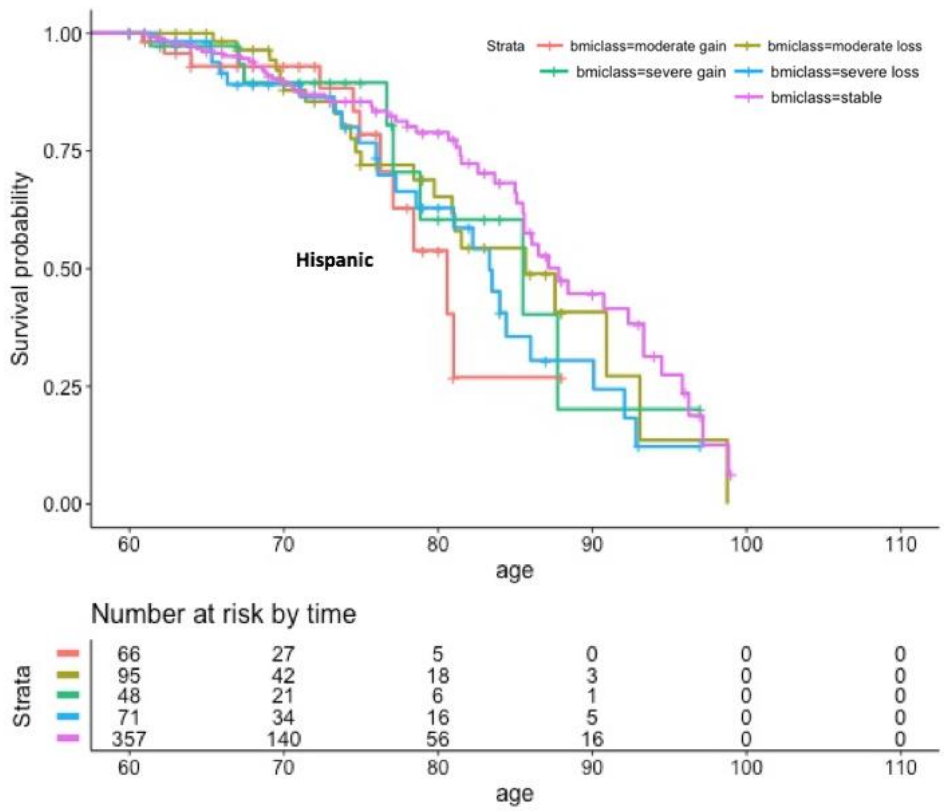
The survival curves of the three races are shown in Figure 3. The curve of severe BMI loss is obviously “below” other curves, which matches the results of the crude model for Caucasian participants. The survival curves of African Americans are overlapping, so BMI change is not related to increased mortality among the African American population. However, the survival curves of Hispanic participant are very discrete, which may be caused by the small sample size of Hispanic people.

**TABLE 5. Effect of Body Mass Index (BMI) Change on Mortality Hazard Ratio (HR) and 95% Confidence Interval (95% CI) by Model, Race and BMI change group.**

| Model | Stable group | Severe Loss | Moderate Loss | Moderate Gain | Severe Gain |
|---|---|---|---|---|---|
| **White** | | | | | |
| Crude Model | 1.00 | 1.14 (1.07, 1.21) | 1.05 (0.98, 1.12) | 1.05 (0.97, 1.15) | 1.00 (0.92, 1.09) |
| Model 1 | 1.00 | 1.12 (1.05, 1.19) | 1.05 (0.98, 1.11) | 1.08 (1.00, 1.18) | 1.06 (0.97, 1.16) |
| Model 2 | 1.00 | 1.19 (1.12, 1.27) | 1.07 (1.01, 1.15) | 1.09 (1.01, 1.19) | 1.15 (1.05, 1.25) |
| Model 3 | 1.00 | 1.12 (1.05, 1.20) | 1.01 (0.95, 1.08) | 1.13 (1.04, 1.23) | 1.17 (1.08, 1.28) |
| Model 4 | 1.00 | 1.13 (1.06, 1.21) | 1.02 (0.95, 1.09) | 1.14 (1.05, 1.24) | 1.17 (1.07, 1.28) |
| **Black** | | | | | |
| Crude Model | 1.00 | 1.10 (0.96, 1.26) | 1.04 (0.89, 1.22) | 1.00 (0.82, 1.21) | 1.09 (0.91, 1.31) |
| Model 1 | 1.00 | 1.08 (0.94, 1.24) | 1.02 (0.87, 1.19) | 1.02 (0.84, 1.24) | 1.12 (0.93, 1.34) |
| Model 2 | 1.00 | 1.09 (0.95, 1.25) | 1.03 (0.88, 1.20) | 1.03 (0.85, 1.25) | 1.13 (0.94, 1.35) |
| Model 3 | 1.00 | 1.04 (0.91, 1.20) | 1.02 (0.88, 1.20) | 1.03 (0.85, 1.25) | 1.07 (0.89, 1.28) |
| Model 4 | 1.00 | 1.07 (0.93, 1.23) | 1.02 (0.87, 1.20) | 1.03 (0.84, 1.25) | 1.09 (0.91, 1.31) |
| **Hispanic** | | | | | |
| Crude Model | 1.00 | 1.69 (1.04, 2.75) | 1.33 (0.81, 2.19) | 1.92 (0.99, 3.71) | 1.23 (0.58, 2.58) |
| Model 1 | 1.00 | 1.67 (1.02, 2.72) | 1.31 (0.79, 2.16) | 1.93 (1.00, 3.75) | 1.25 (0.59, 2.62) |
| Model 2 | 1.00 | 1.93 (1.16, 3.21) | 1.52 (0.91, 2.55) | 2.15 (1.10, 4.20) | 1.59 (0.74, 3.44) |
| Model 3 | 1.00 | 1.71 (1.01, 2.89) | 1.30 (0.76, 2.20) | 1.87 (0.95, 3.67) | 1.52 (0.70, 3.32) |
| Model 4 | 1.00 | 2.09 (1.22, 3.58) | 1.12 (0.64, 1.95) | 1.85 (0.93, 3.65) | 1.36 (0.61, 3.01) |

**FIGURE 3. Survival plot for weight change groups by race**




Strata
bmiclass=moderate gain
bmiclass=moderate loss
bmiclass=severe gain
bmiclass=severe loss
bmiclass=stable
Survival probability
1.00
0.75
0.50
0.25
0.00
Hispanic
60
70
80
90
100
110
age
Number at risk by time
Strata
66 27 5 0 0 0
95 42 18 3 0 0
48 21 6 1 0 0
71 34 16 5 0 0
357 140 56 16 0 0
60
70
80
90
100
110
age

# CHAPTER V. DISCUSSION

The study shows that short-term BMI change is a risk factor for mortality among the middle-aged and older populations in the United States. The effect size depends on the magnitude and direction of BMI change, as well as gender, race, and initial BMI. In our study, BMI loss of 10% or more and BMI gain of 5% or more have stronger effect on mortality. People who have more than 10% BMI gain or loss have the highest risk of mortality. The participants with 5% to 10% BMI gain also have a higher risk of death compare with those with stable BMI. These findings illustrate the importance of monitoring weight closely for people with any initial BMI level. BMI changes of 10% or more in short term are associated with most geriatric syndromes, and behavioral, social factors related to poorer health. People with weight gain always have a higher prevalence of disability or other factors which make them at risk of being less active than those with stable weight (49). In order to minimize confounding from different initial BMI and unintentional weight change due to diseases and undiagnosed poor health condition, we adjusted initial BMI, self-rated health condition, mobility score, and five common chronic diseases. The observed severe BMI loss-mortality association and BMI gain-mortality association still exist, which suggests that unmeasured confounding factors which can dissipate the associations are unlikely to exist unless the confounders have both the high prevalence and strong effects on mortality to reverse the BMI changes.

To sum it all up, compared with stable BMI, BMI gain and severe BMI loss are indicators of higher death rate among the middle-aged and older people in the US. The severe BMI loss-mortality association is proved by many epidemiological studies (50-56). However, some studies hold an opinion that the weight loss should be distinguished as intentional and unintentional, where people who intend to reduce weight for health promotion and diseases prevention rather than weight-related illnesses are regarded as individuals with intentional weight loss (49). Even though in this case, people with unintentional weight loss have worse health condition than those with intentional weight loss (71), epidemiology studies have not been able to illustrate the significant association between intentional weight loss and lower risk of mortality (61, 72-73). In this study, we don't have direct information showing weight intentionality. However, participants with severe BMI loss have higher prevalence of diabetes, cancer, stroke and heart problem, suggesting that severe BMI loss in our study may be associated with weight-related illnesses rather than diseases prevention. In addition, the participants with severe BMI loss have higher activities of daily living (ADL) score, which means participants with severe BMI loss have less ability to do the physical activity than other BMI groups, indicating that if participants who reduce weight intentionally are unlikely to lose weight by increased physical activity. This infers that severe BMI loss in our study may not be intentional.

Although the magnitude of severe BMI loss-mortality association reducing after adjustment for health-related factors and five common chronic diseases in the final model (Model 4) explains part of the association, but not fully explain. One biological explanation discussed in the literature is that severe weight loss among the middle-aged and older populations may be related to reduced ability to maintain internal environment homeostasis and balance energy, because of age-related anorexia (74). The age-associated anorexia has similar immunological and neuroendocrine characteristics with disease-associated wasting syndromes (75). In our study, people with severe BMI loss have higher ADL score and less energy expenditure, which may be caused by a lower dietary intake (76).

BMI gain-mortality association is observed in our study. This finding contrasts with the majority of studies, which have suggested no elevated mortality risk with BMI or weight gain

(57, 65), but is consistent with some that have found negative associations (64). Andres et al. found large weight gain is related to highest mortality among adults who aged 20 to 99 at baseline, and small weight gain is associated with the lowest mortality (68). We found that an increased mortality risk is associated with BMI gain of 5% or more among the middle-aged and old population. Current literature does not indicate a major effect of weight gain or BMI gain on all-cause mortality among the middle-aged and older populations (18). We also have no clear explanation for the discrepancy, but it is worth noting that, in our study, participants with BMI gain have significantly lower initial BMI. And several studies illustrated the low BMI itself is an important predictor of mortality among the old population (46,77), which may be a possible explanation.

We also conducted subgroup analysis showing the associations between BMI change and mortality within different gender or race groups. We found the observed BMI gain-mortality association and severe BMI loss-mortality association exists among females, which illustrates females are more sensitive than males with respect to the association between BMI change and mortality. Our findings are supported by a study conducted in Sweden, which indicates that the female participants have the higher risk of mortality than males in the same BMI change group (78). Another recent study also suggests similar results that females are frailer than males on the association between weight change and all-cause mortality (63). There is one possible explanation that men have higher levels of neuroendocrine and hormonal factors (testosterone) and higher baseline levels of muscle mass, which may protect them from severe weight change and reaching frailty (79-80). In our study, the female participants have a more discrete BMI change distribution compare with males, which matches the explanation above.

With regard to the racial difference on the association between BMI change and all-cause mortality, we found that Caucasians are the most sensitive race group on the association between BMI change and all-cause mortality than African American and Hispanic people. Three significant associations (severe BMI loss-mortality, moderate BMI gain-mortality, and severe BMI gain-mortality) are observed among Caucasian participants. Only one association (severe BMI loss-mortality) is shown among Hispanic participants. There is no significant association between BMI change and all-cause mortality among African American participants. Even though there is less study focusing on the racial difference of BMI change, there is some indirect supporting evidence. Howard et al. investigated racial differences in socioeconomic status and cause-specific mortality and found that, at old age, both Caucasian men and women are at higher risk of death from some chronic diseases including Chronic Obstructive Pulmonary Disease and ischemic heart disease than African American people (81). Also at older ages, social economic status plays a minor role between different races (81). Given that those chronic diseases are associated with BMI change and mortality, it is necessary to consider those diseases as confounders, which may cause the racial difference on the association between BMI change and mortality. Among the Hispanic group, only the association between severe BMI loss and increased mortality is significant; however, the sample size of the Hispanic population in our study is small, so inferences should be interpreted with caution.

Some limitations should be considered when interpreting our results. Initially, half of the BMI was calculated by measured weight and height and the other half of the BMI was calculated by self-reported weight and height, which may cause information bias. But it is well known that measured weight and height are highly correlated to self-reported height and weight (82), especially among the middle-aged and old population because of decreased cultural pressure to be thin (83-84). Secondly, we do not have information about the cause of death. Research has suggested that magnitude and direction of weight change vary by cause of death (85). Previous studies illustrated that weight loss is a risk factor for heart disease mortality (86-88) and non-cancer mortality (89), but a protective factor for diabetes-related mortality (90). Thirdly, we do not have direct information of weight intentionality. Although we discussed our participants' weight intentionality and speculated most participants with weight loss are unintentional, the weight intentionality is still a potential confounder. In addition, we do not have information about diet and depression, which are important confounders of the association between weight change and mortality.

Despite the limitations, our study has some strengths. First, we have a large sample size and all data are derived from Health and Retirement Study, which is a United States representative survey. Secondly, we used Cox proportional hazard regression analysis, which takes into account the fact that each subject has his or her own entry time into the study. Besides, the Cox proportional hazard model concerns the nature shapes of the underlying survival distribution rather than relying on assumptions (91). Thirdly, we considered and controlled for the effects of many potential confounders, which improved the accuracy and reliability of the results. What's more, we not only assessed the general effects of BMI changes on mortality, but examined gender and racial differences in the associations.

In conclusion, our findings illustrate that severe BMI loss, severe BMI gain, and moderate BMI gain are associated with increased all-cause mortality among the middle-aged and older populations in the United States, but moderate BMI loss is not a risk factor for mortality. The results of subgroup analysis implicate gender and racial differences in the association between BMI change and all-cause mortality, where females are more sensitive than males, Caucasians are more sensitive than African Americans. Public health efforts should encourage weight control among the middle-aged and older population.

## CHAPTER VI. REFERENCES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