EFFECT OF INTENTIONAL WEIGHT LOSS ON MORTALITY BIOMARKERS IN OLDER ADULTS WITH OBESITY

BY

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A Thesis Submitted to the Graduate Faculty of

WAKE FOREST UNIVERSITY GRADUATE SCHOOL OF ARTS AND SCIENCES

in Partial Fulfillment of the Requirements

for the degree of

MASTERS OF SCIENCE

Health and Exercise Science

May, 2018

Winston-Salem, North Carolina

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ACKNOLWEDGEMENTS

I would like to thank:

Dr. Kristen Beavers, for allowing me to present data for this project and for your guidance and support during my two years at Wake Forest. I have grown a tremendous amount as a writer and researcher from working with you and through the experiences you provided. I am grateful and thankful for your incredible mentorship.

Dr. Daniel Beavers, for helping to run the statistics for this project, assisting in my understanding of the analyses and results, and for your support as a member of my thesis committee.

Dr. Michael Berry, for helping me to better understand the lung function data used in this thesis, and for your support as a member of my thesis committee.

Dr. Stephen Kritchevsky, for your feedback and guidance regarding writing and presenting this thesis. You enhanced my knowledge of aging research and challenged me to think more analytically. I am thankful for your help and support as a member of my thesis committee.

The Gerontology Research Lab Staff, Karin Murphy, John Stone, and Heather Gregory, for mentoring me through learning the ELISA and Immulite analysis for the biomarkers used in this thesis.

The Medifast® for Seniors research staff, Beverly Nesbit, Jessica Sheedy, and Sherri Ford, for your dedication to this project.

My fellow HES graduate students, for your support and for making this graduate experience a memorable one.

My family and friends, for your endless love and support throughout this experience. I am so thankful to have all of you and I love you all.

The funding centers for this project, Medifast® Inc., Wake Forest Claude D. Pepper and Older Americans Independence Center, the National Institute on Aging, and the Wake Forest University Department of Health and Exercise Science.

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LIST OF ABBREVIATIONS

BMI: Body Mass Index

CHS: Cardiovascular Health Study

CRP: C-Reactive Protein

DSST: Digit Symbol Substitution Test

FBG: Fasting Blood Glucose

FEV_1: Forced Expiratory Volume in One Second

FVC: Forced Vital Capacity

HAI: Healthy Aging Index

IL-6: Interluekin-6

MMSE: Mini Mental Status Examination

MoCA: Montreal Cognitive Assessment

MRP: Meal Replacement Product

RCT: Randomized Controlled Trials

RD: Registered Dietician

SBP: Systolic Blood Pressure

WL: Weight Loss

WS: Weight Stable

ABSTRACT

PURPOSE: To determine the impact of intentional weight loss (WL) on candidate mortality biomarkers, including the Healthy Aging Index (HAI; range: 0-10; healthiest-unhealthiest).

METHODS: 96 older adults (70.3±3.7 years) with obesity (35.4±3.3 kg/m^2) were randomized into a six month WL (n=47) or weight stability (WS; n=49) program. Weight and HAI score [systolic blood pressure, forced vital capacity (FVC), creatinine, fasting blood glucose (FBG), Montreal Cognitive Assessment] were measured at baseline and follow-up.

RESULTS: Baseline HAI score was 3.2±1.6 points. WL participants lost 6.6±0.4 kg (8.6±0.4% baseline), while weight remained stable in the WS group [(-0.2±0.5 kg); $p<0.01$]. Treatment effect estimates revealed a significant HAI score reduction in the WL group [WL: -0.80 (-1.18, -0.41) vs WS: -0.17 (-0.57, 0.23); $p=0.02$], driven by reduced FBG [WL: -4.31 (-8.22, -0.40) mg/dL vs WS: 1.47 (-2.61, 5.55) mg/dL; $p=0.03$] and marginally increased FVC [WL: 0.11 (-0.02, 0.23) L vs WS: -0.04 (-0.17,0.09) L; $p=0.08$]. In groups combined, 1 kg of WL was associated with a 0.07 (0.01, 0.14) point HAI score reduction ($p=0.03$).

CONCLUSION: Metabolic and pulmonary factors are likely responsible for the net 0.63 point HAI score reduction with intentional WL, consistent with an 11% reduced mortality risk in observational studies.

INTRODUCTION

Associations Between Obesity, Weight loss, and Mortality in Older Adults

The Aging of America

According to the Administration on Aging, 47.8 million Americans were over the age of 65 in 2015, representing 14.9% of the U.S. population. This is more than triple the number of adults over the age of 65 in 1990 (4.1%). Currently, about one in every seven Americans is over the age of 65, with this number continuing to increase, as demonstrated by the 30% (11.1 million) increase in adults over 65 years between 2005 to 2015, compared to the 5.7% increase in those under 65 years of age. The number of adults over 65 years is expected to continue to increase to 82.3 million (21.7%) by the year 2040 (1).

Not only are there more people over the age of 65, individuals 65 years old are living longer with a life expectancy of 19.4 years, ultimately increasing the number of adults in the 65 years and older subgroups. Those aged 65-74 years represent 27.6 million Americans, which is 12 times greater than that age population in 1900; those aged 75-84 years represent 13.9 million Americans, which is 17 times larger than that age population in 1900 (1).

Alongside increasing age of the U.S. population is the increasing number chronic conditions. Three out of every four Americans 65 years and older have more than one chronic condition that limits daily living and requires continuing medical attention, such as arthritis, heart disease, cancer, diabetes, and osteoporosis, with obesity being considered a risk factor for all of these chronic conditions. This creates a financial burden

for the United States, considering about 71% of health care spending goes to caring for individuals with multiple chronic conditions (2).

Obesity is a Common, Severe, and Costly Health Condition

Overweight and obesity are defined as weight higher than what is considered a healthy weight for a particular height with excess adipose tissue, occurring when there is a disparity between energy intake and energy expenditure (3). Diagnosis is typically made using Body Mass Index (BMI), calculated as weight (kg) divided by height (m^2), or total body fat, expressed as a percentage. Individuals with a BMI of 25.0 to <30 kg/m^2 are considered overweight. A BMI of 30 to <35 kg/m^2 is considered Class 1 obesity, 35 to <40 kg/m^2 is Class 2 obesity, and 40 kg/m^2 or higher is Class 3 or severe/extreme obesity (4).

The prevalence of obesity in 2013-2014 was 37.7%, which is 3.4% higher than the prevalence in 2005-2006 (5). Obesity rates vary amongst gender, race and ethnicity, and age. Overall, 40.3% and 41.5% of women and men, respectively, 65-74 years of age were obese from 2007-2010 (6). Among men, there was no difference between race and ethnicity in older adults. Non-Hispanic black women aged 65-74 had the highest prevalence of obesity at 53.9% compared to Non-Hispanic white women at 38.9% (6). Between 2011-2014, individuals aged 40-59 years had the highest prevalence at 40.2%, followed closely behind by those aged $\geq$60 years and 20-39 years at 37% and 32.2%, respectively (7). Amongst older adults, those aged 65-74 had a prevalence of obesity of 40.8%, compared to 27.8% of those aged 75 years and older in both men and women (6).

Collectively, obesity itself and the complications from obesity result in severe direct and indirect (*i.e.* lost productivity, insurance, etc.) economic cost. It was estimated that in 2006, individuals who were obese spent about 42% more on medical care costs compared to normal weight individuals (8). In 2003, it was estimated that a total of $73 billion was spent in medical expenditures, with only half of that paid for through Medicare and Medicaid (9). These costs are expected to increase by $48-66 billion per year by the year 2030 (10), representing the alarming impact of obesity on health as well as the economy.

Interplay between Aging, Obesity, and Mortality

The severity of obesity on mortality is reflected in a meta-analytic study of 10,625,411 individuals from 4 continents, which demonstrated that individuals who were slightly overweight (BMI: 25.0-<27.5 kg/m^2) or overweight (BMI: 27.5-<30.0 kg/m^2) had a 1.07 and 1.20 times greater chance of death compared to normal weight individuals (BMI: 20.0-<25.0 kg/m^2). Moreover, Class 1, 2, and 3 obese individuals were at 1.45, 1.94, and 2.76 times greater chance of mortality, respectively, compared to normal weight individuals (11). Those who are overweight or obese are also at an increased risk for many health conditions including hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, etc. (3). Evidence likewise suggests that obesity negatively impacts several biomarkers, including blood glucose, interleukin-6, Cystatin-C, etc., suggesting obesity collectively influences multiple systems, as discussed further in the following “Introduction to the Health Aging Index” section.

Collectively, evidence demonstrates that mortality risk increases with increased BMI in individuals aged 30 to 70 years of age (12–14), but the impact of obesity on mortality decreases with age. For example, a prospective cohort of 6,053 obese individuals showed that in men, the standard mortality ratios for those 18-29, 30-39, 40-49, and 50-74 were 2.46, 2.30, 1.99, and 1.31, respectively. For women in the same age categories, the standard mortality ratios were 1.81, 2.10, 1.70, and 1.26, respectively (13). Some argue that obesity may be a protective measure for older adults. For example, Childers and Allison argue that obesity in older adults may be protective during illness (15), as the extra adiposity could provide additional energy reserve (16). Evidence also exists in support of an osteoprotective effect of mild obesity, due to increased bone mineral density among those who are obese, decreased risk of fractures and osteoporosis compared to those who are underweight (17), as increased cushioning during a fall. Additionally, several epidemiological studies have demonstrated that being overweight or obese later in life does not increase mortality (16). Nonetheless, frailty and decreased physical function can result from obesity in older adults (18). Additional health concerns associated with obesity earlier in life still apply later in life, with the added risk of sarcopenic obesity (large amounts of fat with loss of muscle mass), which is why clinicians may be inclined to prescribe weight loss in older adults, considering the detrimental effects of obesity and the strong recommendation for weight loss in younger adults. The controversy lies in that obesity can have potential detrimental effects on health, yet it does appear to provide some benefit in older adults.

Introduction to the Healthy Aging Index

The Healthy Aging Index (HAI) was originally derived from the "physiologic index of comorbidity," coined in 2008 by Newman et al. Originally, the index used non-invasive tests for carotid wall thickness (vascular ultrasound), pulmonary function [Forced Expiratory Volume in one second (FEV_1) and Forced Vital Capacity (FVC)], white matter grade (brain MRI), glucose metabolism [fasting blood glucose (FBG)], and kidney function testing (serum Cystatin-C) to detect subclinical disease and distinguish very high and very low levels of disease in community-dwelling older adults participating in the Cardiovascular Health Study (CHS) (19). Each variable was scored based on tertiles (except FBG, in which case clinical cut points were used), with a 0 being the healthiest and a 2 being the unhealthiest. Component scores were added up to give a total score on the physiologic index of comorbidity of 0-10. In the seminal publication, this index was found to be a stronger predictor of morbidity and mortality compared to age itself, thus, representing biological age rather than chronological age. Specifically, participants in the highest score category of index score (7-10) had a 3.80, 1.93, and 1.48 times greater chance of mortality, mobility limitations, and difficulty with activity of daily living, respectively, compared to individuals with a score of 0-2, thus indicating that disease-free survival is important for exceptional survival (19). Subsequently, this index has been used to show that disease burden (as indicated through the physiologic index) is independently associated with frailty (20) and higher scores are associated with slower gait speed and greater decline in gait speed (21).

Although measures in the physiologic index of comorbidity predicted mortality and chronic disease, some component measures are not commonly used in epidemiologic

studies. To increase its clinical utility, in 2012, Sanders et al. developed a modified physiologic index using more frequently used measures, such as blood pressure (in place of carotid intima-media thickness) and the Digit Symbol Substitution Test (DSST, in place of the MRI-acquired white matter grade), in addition to spirometry (FEV_1 and FVC), FBG, and serum Cystatin-C. This modified physiologic index served as a model for the HAI, with surrogate measures used in the HAI, such as the Modified Mini Mental Status Examination (MMSE) and serum creatinine, based on measures available from the study cohort. As with the original physiologic index, the modified index was a better predictor of death than age alone and those with a score of 7-10 had a 3.53 and 1.22 times greater chance of mortality and incident disability, respectively, compared to those with a score of 0-2 (22).

Building on prior work by Newman, Sanders, and others, in 2014 the HAI was formally created (23) and included functional scores in five different organ systems: systolic blood pressure (SBP), FVC, creatinine, FBG, and the MMSE. Sanders and colleagues used the CHS to examine how well the HAI could predict death. Additionally, authors used the Long Life Family Study to determine the heritability of the HAI, considering the HAI would be able to identify individuals with exceptional survival. Compared to the results of Sanders et al. (2012), unlike the physiologic index, the HAI was slightly worse at predicting death compared to age, but together, age and the HAI predicted death exceptionally well. With every unit increase of the HAI, there was a 1.17 times greater risk of death. Those with a score of 7-10 were at 2.62 times greater risk of death compared to those with a score of 0-2. Results from the Long Life Family Study analysis indicated that the HAI demonstrated moderate to high heritability (23), which

led to further research in looking at genes and genetic variants associated with longevity (24,25).

Further research has confirmed the association of the HAI with mortality in various cohorts (26,27), while also adding to the literature the association between increased HAI score and increased cardiovascular disease (26) and cardiovascular mortality (27) (but not with cancer (26,27)). McCabe et al. (2016) additionally showed that adding C-Reactive Protein (CRP) and heart rate to the HAI helped to identify healthy versus unhealthy older adults (26). Moreover, Wu et al. (2017) found that using self-reported respiratory problems and the DSST resulted in comparable associations with mortality in a nationally-representative sample (27). Consequently, the HAI is becoming recognized as a robust predictor of mortality and cardiovascular disease in multiple cohorts of older adults using measures commonly utilized clinically and in research. Subsequent paragraphs explore the association between individual HAI components with mortality, age, and weight.

Mortality Biomarkers

Healthy Aging Index and Other Candidate Mortality Biomarkers

HAI component variables include: SBP, FVC, creatinine, FBG, and the MMSE, all of which are easily-measured physiologic variables targeting various organ systems. However, the Montreal Cognitive Assessment (MoCA) tool was utilized in place of the MMSE in the present analysis. Both MMSE and MoCA are quick screening tools for mild cognitive impairment, but the MoCA has demonstrated slight superior sensitivity

and specificity for mild cognitive impairment and Alzheimer's disease (28,29). Other candidate mortality biomarkers are known or thought to be associated with mortality and include: gait speed, grip strength, the DSST, FEV_1, Interleukin-6 (IL-6), CRP, and Cystatin-C, which are also measure of various physiologic functions.

The following sections describe the HAI component variables and candidate mortality biomarkers, and provide a review of the literature associating each variable with age, weight, and weight loss. A summary of the normal ranges and the review of literature for each variable can be found in **Table I.**

Table I: Mortality Biomarkers Their Normal Ranges and Association with Age, Weight, and Weight Loss.

	Normal Range	**Age**	**Weight**	**Intentional Weight Loss**
SBP (mmHg)	90-120	↑ After age 50 ↓ After age 75	↑	↓
FVC (L)	Median: 3.8	↓	↓	↑
Creatinine (mg/dL)	<0.89	↑	↑	Unclear
FBG (mg/dL)	<100	↑	↑	↓
MoCA (0-30)	26-30	↓	↓	Unclear
Gait speed (m/s)	>0.8	↓	↓	↑
Grip strength (kg)	>21 women >37 men	↓	↑	↑
DSST (0-93)	>26	↑	↓	Unclear
FEV_1 (L)	4L (90% predicted)	↓	↓	↔
IL-6 (pg/mL)	<2.5	↑	↑	↓
CRP (mg/L)	<1	↑	↑	↓
Cystatin-C (mg/L)	<1.03	↑	↑	↓

*Arrow size indicates strength of association

Systolic Blood Pressure

SBP is the amount of pressure on the arteries when the heart is contracting. A SBP of less than 90 mmHg is considered low (hypotension) (30), 90-120 mmHg is normal, 120-139 is prehypertensive, and anything 140 mmHg or greater is considered hypertensive (31).

Most, if not all (32), studies found associated elevations in SBP with mortality. For example, results from the Helsinki Businessmen Study (including 3,267 men born between 1919 and 1934 and followed through 2012) found that high baseline blood pressure of 140-159 mmHg or $\geq$160 mmHg was associated with 1.45 times and 2.21 times increased risk of all-cause mortality compared to those with normal blood pressures (<120 mmHg) (33). This study also reported that men with a blood pressure of 140-159 mmHg and $\geq$160 mmHg were a 1.79 and 3.91 times greater risk of cardiovascular mortality compared to those with a SBP of less than 120 mmHg.

SBP pressure is known to increase with age after the age of 50 (34) and up until age 75, at which point SBP decreases (35,36). Likewise, as weight increases, so does SBP. An 11-year prospective study of 15,971 men and 13,846 women aged 20 years and older demonstrated that higher BMI increased SBP, with the strongest association in the oldest individuals. Those aged 50 years and older at baseline who increased BMI (BMI increased > 0.1 kg/m^2 every follow-up year) at follow-up had a 1.5 times greater chance of developing hypertension (37). Other studies have shown similar relationships between BMI and SBP (38,39). In terms of weight loss, the ENCORE study (n=144, >35 years) demonstrated a decrease in SBP by 11.7 mmHg with weight loss and diet interventions compared to 3.9 mmHg decrease in the usual care group (40).

Clinical trial data also support the role of weight change and reducing the incidence of hypertension. In the Nurses' Health Study, women who gained more than 25 kg since the baseline visit in 1976 were at 2.85 times the risk of developing hypertension compared to those who lost or gained less than 2 kg (39). A Randomized Controlled Trial (RCT) of 975 men and women aged 60-80 years on antihypertensive medication demonstrated that obese individuals assigned to weight loss had a 30% reduced risk of continuing to use antihypertensive medication or experiencing a cardiovascular event compared to those not assigned to weight loss. During the follow-up (15-36 months), those assigned to weight loss were at a 63% reduced risk of using antihypertensive drugs or experiencing a cardiovascular event (41). Consequently, weight loss can help reduce the burden of high blood pressure or hypertension in older adults who are overweight or obese.

Forced Vital Capacity and Forced Expiratory Volume in one Second

FVC and FEV_1 are both lung function tests that measure the volume of air maximally exhaled and the amount of forcefully expired air in one second, respectively. Normally about 80% of air (3.8 L) can be forcefully expired (42). However, lung function test data are typically values are presented as a percent of predicted (100 x observed/predicted) from a validated equation using age, sex, race, and height (43,44). Median reference values are considered to be 100%, with the range of normal values being ±2 standard deviations (80-120%) for those 15-35 years of age, and ±3 standard deviations (70-130%) for young children and older adults (45). Obstructive lung disease is typically diagnosed using the FEV_1/FVC ratio, with values less than 0.7 indicating lung

disease (46). Moreover, higher FEV_1 scores are associated with greater cognitive and physical function in non-COPD patients (47). A longitudinal study of 522 older adults (80 years and older) revealed those in the lowest quartile for FEV_1 score (<1.27 L) had a 92% greater risk of death than the rest of participants with an FEV_1 score >1.27 L (48).

Age plays a role in decreasing of pulmonary function values (45). According to the American Lung Association, FVC decreases by about 0.2 L every decade and FEV_1 decreases by 1-2% every year after the age of 25 (42). A longitudinal study of 4,829 participants aged 50 to 74 years showed a decrease in FEV_1 score by 0.21 liters in men and 0.19 liters in women with every one standard deviation increase in age (6 years) (47). Another longitudinal study revealed a decrease of 38 mL/y and 32 mL/y decrease in FEV_1 and FVC with age, respectively. FVC starts to decline later in life compared to FEV_1, which correspondingly causes the FEV_1/FVC ratio to fall as well (49).

Additionally, increases in fat mass are associated with decreases in FEV_1 and FVC. The Healthy Aging and Body Composition study examined changes in FEV_1 and FVC in conjunction with changes in body composition in 957 men and 1,024 women aged 70-79 over a 5-year period. Cross-sectional analyses at baseline revealed a positive relationship between FEV_1 and FVC with total thigh muscle area and a negative relationship with visceral adipose tissue. Longitudinal results showed that increases in fat mass were significantly associated with decreases in both FEV_1 and FVC. Men and women who gained weight decreased FEV_1 by 11.67% and 10.92%, respectively, and decreased FVC by 8.01% for both men and women (50). Similarly, another longitudinal study of 47 women and 30 men over a 7-year follow-up period showed that a one cm increase in sagittal abdominal diameter predicted a decrease in FEV_1 and FVC by 31 and

46 mL respectively (51). Nonetheless, weight loss may improve pulmonary function in older obese men, as demonstrated by a small weight loss study. Thirty-five men in the weight-loss arm experienced a 3% increase in FVC after a 9-month diet period whereas the control group did not experience any changes in FEV_1 (52). However, additional evidence is limited supporting the claim that weight loss improves pulmonary function in healthy older adults.

Creatinine and Cystatin-C

Creatinine and Cystatin-C are blood-based biomarkers which are used clinically to estimate glomerular filtration rate (GFR) – an indicator of kidney function and disease. Values for Creatinine and Cystatin-C are not typically reported as raw data, but used in equations to estimate GFR. Suggested references ranges for creatinine are 0.6-1.1 mg/dL for women and 0.7-1.3 mg/dL in men (53). A small study of 309 individuals suggested the 95% reference range for Cystatin-C in those 50 years older is between 0.58-1.02 (54). However, data from the CHS showed median creatinine and Cystatin-C was 0.89 mg/dL and 1.03 mg/L (55), respectively, and those with Cystatin-C values above 0.89 mg/L were at an increased risk of death, with each successive increase in quantile range increasing mortality risk (56), suggesting lower scores are better. Nonetheless, chronic kidney disease can be defined as an GFR of less than 60 ml per minute per 1.73 m^2 of body-surface area (57) using creatinine to estimate. When analyzed by Cystatin-C or Cystatin-C in combination with creatinine, the cut-point for chronic kidney disease increases to a GFR value less than 85 ml per minute per 1.73 m^2 (58).

It is well recognized that kidney dysfunction is associated with increased cardiovascular morbidity and mortality, and higher Cystatin-C and creatinine levels are also associated with greater risk of death. For example, analysis of 4,637 community-dwelling older adults participating in the CHS found that individuals with the highest values of Cystatin-C ($\geq$1.60 mg/L) were 2.58 times more likely to die from all causes and 2.83 times more likely to die from cardiac events compared to those with the lowest Cystatin-C values ($\leq$0.89 mg/liter). Likewise, individuals who presented with the highest category of creatinine levels ($\geq$1.56 mg/dl men and 1.16 mg/dl for women) were 1.48 times more likely to die from all causes compared to those with the lowest creatinine values ($\leq$0.85 mg/dl men and 0.65 mg/dl for women) (56).

Kidney function declines with age, as shown through longitudinal data in 10,184 participants aged 66 years old, which revealed an annual decline in GFR of 1.4 and 0.8 ml/min/1.73 m^2 for men and women, respectively (59). Likewise, a study of 98,688 individuals 20-94 years old found that serum creatinine levels started increasing at age 40 in females and age 60 in males, reaching values of 1.10 and 1.28 for women and men, respectively (60). Cystatin-C values also increase with age, as demonstrated in a combined analysis of the CHS, Health ABC, MES, and PREVEND studies. Healthy adults aged 80 years and older had a Cystatin-C concentration of 1.06 mg/L while younger individuals less than 40 years had values of 0.72 mg/L (61). Although obesity is a well described risk factor for many chronic diseases, the impact of weight on kidney function is unclear. For example, overweight and obese individuals participating in the Hypertension Detection and Follow-up Program study had a 21% and 40% increased risk of developing chronic kidney disease, respectively (62); however, data from 2,676

participants in the Framingham Heart Study Offspring did not show a significant difference between the incidence of chronic kidney disease among overweight and obese individuals relative to normal weight individuals (63). Meanwhile, cross-sectional studies show a positive association between weight (64), as well as fat mass (65), with Cystatin-C.

Similarly, the impact of weight loss on kidney function among adults with obesity is also unclear. A study of 318 participants 40-65 years of age, who lost an average of 4.0 kg, demonstrated improvements in GFR by 4-5%, regardless of dietary approach (66). Conversely, a study of 115 overweight and obese individuals with type 2 diabetes who lost an average of 9.3 kg decreased GFR by 4 and 2 ml/min/1.73 m^2 for each diet group. Serum creatinine, however, increased by 1 to 3 μmol/L (67). Few studies have examined the impact of weight change on creatinine and Cystatin-C alone. A small study of Japanese men showed a positive correlation between fat mass and serum creatinine (68). One study of 207 participants (18-65 years) demonstrated that both a low-carbohydrate and low-fat diet reduced serum creatinine and Cystatin-C levels by about 1% after 2 years in healthy adults with creatinine and Cystatin-C values within the normal ranges at the beginning of the study (69). Yet more large-scale RCT data are needed to determine the effect of weight loss on creatinine and Cystatin-C, particularly among older adults with obesity.

Fasting Blood Glucose

As the name suggests, FBG measures the amount of sugar (or glucose) in blood after a period of fasting (typically 8-12 hours). Normal FBG levels are below 100 mg/dL, with values between 100-125 mg/dL and greater than 126 mg/dL considered prediabetic and diabetic, respectively (70). Conversely, hypoglycemia (low blood sugar) is typically considered a value less than 70 mg/dL for people with diabetes (70) and below 55 mg/dL for people without diabetes (71). Diabetes can result in additional complications such as skin complications, glaucoma, neuropathy, kidney disease, stroke, heart disease, etc. (72). The incidence and prevalence of diabetes increased by 23% and 62%, respectively, between 1994-1995 and 2003-2004 (73), and it is currently 7th leading cause of death in the United States (74). Recent data show that individuals with diabetes are at almost twice the risk of death compared to individuals of the same age without diabetes (74), which can be attributed to diabetes-related complications (75) and glucose dysregulation, itself. For example, a study of 2,300 diabetic and nondiabetic individuals aged 18-64 years found that those with the lowest glucose levels (about 50 mg/dL) were at 3.22 times risk of all-cause mortality compared to those with a FBG level of about 100 mg/dL. Similarly, those with known diabetes were at 4.17 and 6.17 times greater risk for all-cause and cardiovascular mortality, respectively, compared to those with FBG levels of about 100 mg/dL (76).

According to the CDC, age is one of the many risk factor for diabetes, with the greatest prevalence seen in those 65 years and older (77) .In 2014, 15.2% of individuals aged 45-64 years were diagnosed with diabetes compared with 25.9% of individuals aged 65 years and older.(78) Data from the 1999-2002 NHANES survey of 2,809 individuals

revealed that about 60.6% and 39.4% of older adults (65+ years) had middle-age-onset diabetes and elderly onset diabetes, respectively, with more individuals at middle-age going undiagnosed. Additionally, elderly individuals with middle-age-onset diabetes had higher FBG levels (172.4 mg/dL) compared to those without middle-age-onset diabetes (132.3 mg/dL, $p = 0.001$) (79).

Weight is also associated with increased risk for diabetes. A study of 340,234 individuals in the InterAct, prospective, case-cohort study aged 18 years and older followed between 1991 and 2007 found that those with a BMI of 25.0-29.9 kg/m^2 had a 2.84 and 3.81 times greater chance of developing type 2 diabetes for men and women, respectively. Individuals with a BMI of greater than 30 kg/m^2 had 7.58 and 11.6 times greater chance for developing type 2 diabetes for men and women, respectively. Likewise, the InterAct study reported a near doubling in the risk of developing type 2 diabetes associated with every one standard deviation increase in BMI (3.6 kg/m^2 for men and 4.4 kg/m^2 for women). Body composition distribution was also predictive with every one standard deviation increase in waist circumference (10.0 cm for men, 11.2 cm for women) associated with 1.95 and 2.43 times greater chance of developing type 2 diabetes for men and women, respectively (80).

Encouragingly, several studies demonstrate that weight loss can reduce the incidence of diabetes and decrease FBG levels, even among older adults. Seminal findings from Diabetes Prevention Program showed that 7-10% weight loss reduced the incidence of diabetes onset by 58% compared to placebo, and importantly, of a similar magnitude as pharmacotherapy. The largest reduction in incidence compared to placebo was observed in individuals older than 65 years of age, with similar results seen in the

lifestyle (71%) and pharmacologic (69%) groups (81). Notably, these interventions are effective in real-world settings, with a weight loss of about 2.12 kg resulting in a decrease in glucose of about 1.80 mg/dL (82). Additionally, studies have found that 5-10% weight loss is associated with a reduction in FBG on the order of 4.3 mg/dL or hemoglobin HbA1c (another blood glucose marker) from about 7.3% to about 6.6% (diabetes range 6.5% and over) (83,84).

Montreal Cognitive Assessment and Digit Symbol Substitution Test

The MoCA and the DSST are objective assessments used to measure cognitive functioning. The MoCA is a 16 item, 11-category test used to identify individuals with mild cognitive impairment and for the diagnosis of Parkinson's Disease, stroke, and other cognitive deficiencies (85). Domains tested include naming, memory, attention, language, orientation, abstraction, visuospatial and executive function (85). The highest possible total score is a 30 and those scoring below 26 are considered to have mild cognitive impairment (86). The DSST also evaluates cognitive function by evaluating response speed, sustained attention, visual spatial skills and set measures of intelligence. During a 120-second period, the individual must fill in a series of symbols that correspond to a set of digits. Higher scores (number correct) are indicative of better performance (87), with scores ranging from 0-93 (88). A longitudinal study of 5,888 older (mean age 75.1 years) individuals in the CHS showed that those in the lowest quartile/worst DSST scores (score of $\leq$29) were at a 2 times greater risk of developing clinical or subclinical disease compared to those in the highest quartile/best score (score of >48) (89). As demonstrated in a study of 9,399 individuals with a mean age of 57 and 65 years at 3 and 6 years

follow-up in the Atherosclerosis Risk in Communities Study, risk of developing Alzheimer's Disease was 2.5 to 3.5 times higher in individuals with lower DSST scores (0-<39) compared to those with highest DSST scores (51-93). Moreover, those who dropped to the lowest tertile (0-<31) at 6-years follow-up from the highest tertile (51-93) at 3-years follow-up had an 11-fold increase in the risk of developing Alzheimer's Disease (90). Additionally, individuals who scored >40 cut their risk of death in half compared to those with a score of <18, with scores above 26 signifying a protective effect on mortality (91).

Advanced age has long been recognized as a risk factor for cognitive decline (92), with recent evidence implicating obesity – particularly abdominal obesity in middle age – in its pathogenesis. To demonstrate, a study of 6,583 participants showed that obesity in midlife (40-45 years) was associated with increased risk for dementia after a 36-year follow-up. Interestingly, those categorized in the highest quintile of sagittal abdominal diameter (24.5-40.0 cm men, 23.2-40.0 cm women) were at almost a 2-fold increased risk of dementia compared to those in the lowest quintile (10-19.4 cm men, 10-17.5 cm women), independent of BMI (89). That said, the association between obesity and cognitive function may vary by age (94), with conflicting results reported among older (*i.e.* 65+ years) adults. For example, a study of 382 older women demonstrated every one unit increase in BMI at age 70 was associated with a 1.13 times and 1.15 times greater risk of developing Alzheimer's disease at ages 75 and 79, respectively (95). Conversely, data from a sample of 2,798 older adults (65-97 years) participating in the CHS and followed for an average of 5.4 years revealed an inverse relationship between BMI later in life and dementia. Authors reported obesity resulted in a 37% reduced risk of dementia

compared to normal weight individuals, and being underweight increased the risk of dementia by 62% compared to normal weight individuals (96). Investigators speculate this difference may be attributed to unintentional weight loss due to disease in older adults (96). However, as with other traditional disease risk factors (*i.e.*, cholesterol, HbA1c), it is all together reasonable that advanced age itself may diminish or invert the strength of association between the risk factor (obesity) and disease (cognitive decline).

Studies examining the association between change in weight and cognitive decline are few in number, with equivocal findings reported. In 2,283 postmenopausal women (65-79 years) participating in the Women's Health Initiative, researchers showed that among those who remained weight stable or gained weight after 5.4 years of follow-up did not experience changes in cognitive performance; however, those who lost weight experienced significant declines in cognition (97). Conversely, recent findings from the LookAHEAD showed intentional weight loss over a 10 year period did not impact performance on a cognitive assessment battery (including overall learning and memory, processing speed, executive function and global cognitive function) (98). Results from these studies highlight discrepancies in the current literature and indicate a clear need for well-designed trials to elucidate the true impact of intentional weight loss on cognitive function in older adults with obesity.

Gait Speed

Gait speed is defined as distance walked divided by the time it takes to walk that distance. It is associated with survival (99) and it tracks with grip strength, while also

being used to define mobility impairments (100). A speed slower than 0.8 m/s is considered clinically meaningful (99), as it is strongly associated with mortality (101). Importantly, individuals with a faster annual decline in gait speed (20%; -0.024 m/s) are more likely to experience disability than those who maintain walking speed (102). Moreover, a recent meta-analytic work demonstrates significantly increased survival with every 0.1 m/s increase in gait speed (99) .

Individuals with slower gait speeds tend to be older (103) and obese (104). Gait speed slows by about 0.017 m/s every year (102). A longitudinal study of 4,007 older adults (65-85 years) found a decrease in gait speed was more prominent in obese adults compared to normal weight adults, with obese individuals experiencing a 45% accelerated decrease in walking speed compared to normal weight individuals (104). Additionally, another longitudinal study (25-year follow-up) of 6,229 adults aged 45-64 years demonstrated individuals with normal BMI at the start of the study, but who had an increase in BMI both from 0-10 years and 10-25 years follow-up (final BMI = 27.2 kg/m^2) had a gait speed of 0.949 m/s compared to individuals who maintained a normal BMI (22.5 kg/m^2) with a gait speed of 0.968 m/s (p <0.001).(103) Although few in number, RCT evidence demonstrates that weight loss of 7-10% over at least 12 months can improve gait speed by roughly 0.05 m/s, when compared to weight stability (105,106). Importantly, this magnitude is considered a small, clinically meaningful change (107) and is likely driven by weight loss associated reductions in fat mass (108), with change in intramuscular fat deposition, likely important (109).

Grip Strength

Handgrip strength is a clinical indicator of overall body strength (110), with higher scores positively associated with better physical function (111). Grip strength performance has been incorporated into recent sarcopenia cutpoints (112), with values less than 37 kg for men and 21 kg for women associated with increased likelihood for presenting with mobility limitations (*i.e.* walking <0.5 m/s and difficulty climbing stairs) (113). Low grip strength is also associated with an increased risk of hospitalization (114), morbidity (115), and mortality (116). In a sample of 919 women from the Women's Health and Aging Study, congestive heart failure was more common in those with lower grip strength scores, with a clear gradient between highest (> 22 kg) and lowest grip strength ($\leq$18 kg) tertiles and lower grip strength conferring twice the risk of death (115). Similarly, a data set from a large (n=3594) prospective cohort study demonstrated those in the highest tertile for handgrip had an 11% reduction in mortality in individuals aged 50-69, and a 14% reduction in mortality for those aged 70 and older (116), thereby indicating the importance of hand grip strength scores as a predictor for mortality, especially among older adults.

Grip strength is an important biomarker for aging across the lifespan (117), with a decrease in 1% of grip strength with every year after mid-life (118). To illustrate, data coming from a cross-sectional study of 5,877 adults over the age of 50 demonstrated that men and women 50-59 years had higher hand grip strengths (males: 45.1 kg, female: 27.1 kg) compared to those 80 and older (males: 29.0 kg, females: 17.5 kg) (119). Furthermore, a longitudinal study of 292 men and women born between 1920-30 showed those in the 5th percentile at baseline decreased grip strength by 1.34 kg/year for men and

0.80 kg for women. Conversely, those in the 95th percentile at baseline increased grip strength by 0.91 kg/year in men and 0.80 kg/year in women after a 10-year follow-up (120).

Likewise, weight is a strong, independent predictor of grip strength (118). Overweight women over the age of 80 have slightly higher hand grip strengths (147.8 N for overweight compared to 136.1 N for normal weight), which is likely driven by increased lean mass (111). However, despite positive associations between grip strength and weight, weight loss, when combined with exercise and adequate protein, may actually increase grip strength in older adults. An RCT of 80 overweight or obese adults over 55 years who underwent a resistance training program and who consumed either an isocaloric diet (control) or high protein diet showed increases in hand grip strength. Specifically, both groups lost weight (3.4 and 2.8 kg) and increased grip strength by 2.0 and 2.2 kg for the protein and isocaloric diet group, respectively (121). However, other findings suggest that intentional weight loss via high protein or standard protein diet in older adults decreased grip strength by 1.9 and 1.4 kg, respectively (122), thus demonstrating inconclusive evidence on the influence of weight loss on hand grip strength in older adults.

Interleukin-6

IL-6 is one of the 23 currently known interleukins involved in the immune response with elevations implicated in the onset and progression of many diseases including CVD, cancer and multiple sclerosis (123). Of note, IL-6 precedes CRP in the

inflammatory process, leading to a 10 to 100 fold increase in systemic concentration of the acute phase reactant (124). Accordingly, IL-6 is also recognized as a key contributor in the development of coronary heart disease.

Clinically, circulating of IL-6 concentration less than 2.5 pg/mL are considered desirable for functional outcomes (125). For example, in a prospective study of 404 healthy men (20-84 years), those in highest quartile of serum IL-6 (>2.28 pg/mL) were found to be at 2.3 times the risk of having a myocardial infarction compared to those in the lowest quartile (<1.04 pg/mL) (126). Similarly, in a prospective study of adults aged 71 years and older (n=588), adjusted odds of developing mobility disability were 1.67 times higher in the highest IL-6 quartile (>2.51 pg/mL) compared to the lowest quartile (<1.58 pg/mL) (127). Similarly, IL-6 concentrations higher than 2.51 pg/mL resulted in a 1.66 times greater odds of developing disability with activities of daily living compared to individuals with IL-6 concentrations below 2.51 pg/L (127). Elevated IL-6 is also an independent predictor of increased mortality risk (128), particularly in old age (129), where each standard deviation increase in IL-6 associated with a 1 year reduction in lifespan for both men and women. Notably, this association appears non-linear with those above the 3rd quartile (3.3 pg/L) of IL-6 experiencing a 6.8% mortality rate compared to 1.0% in the 1st quartile (1.3 pg/L) after a 3 year follow-up period (130).

Both obesity and age are associated with increases in IL-6 values. Evidence from the MacArthur Studies of Successful Aging showed a linear relationship between age and IL-6 levels (131), with men having higher values compared to women (132). Recent data from the PolSenior Study showed that adults aged 65-69, had systemic IL-6 concentrations of 1.8 pg/mL, compared to those 90 or older who had clinically unhealthy

concentrations averaging 3.5 pg/mL (130). Because one third of circulating IL-6 is produced by adipose tissue (133), higher levels of IL-6 are also associated with obesity (133–135), regardless of age (136). Encouragingly, however, obesity-related elevations in IL-6 appear modifiable through weight loss. Data coming from a large (n=454), 18-month RCT conducted at Wake Forest University show intentional weight loss in older adults (resulting from diet alone or diet plus exercise) significantly reduced in IL-6 compared to a weight stable exercise control group (D+E: -0.5±15%, D: -0.5±16% versus E: 0.1±0%; $p = 0.008$) (137). A dose-response was observed (*i.e.*, greater weight loss yielding greater reductions in IL-6), with 5% reduction in body mass resulting in significantly increased odds of achieving clinically healthy (i.e. <2.5 pg/dL) levels of IL-6 (138) .Thus, weight loss in older adults can aid in reducing circulating IL-6, which may ultimately reduce onset and progression of several adverse health conditions, including mortality.

C-Reactive Protein

CRP is a plasma protein produced in the liver, measured in the blood, and used as a clinical marker of inflammation. Results of less than 1 mg/L, 1-3 mg/L, and greater than 3 mg/L are considered low, moderate, and high risk of cardiovascular disease, respectively (124,139). Accordingly, higher levels of CRP are associated with increased number of cardiovascular deaths (124,140), particularly among the elderly (129).

Advanced age and high BMI are both associated with increased CRP levels. People over the age of 65 tend to have greater levels compared to those younger than 65,

with levels of CRP gradually increasing by decade of life (i.e. 20-30 years old have CRP levels of 1.24 mg/L, compared to those 60-70 and 70-80 with CRP levels of 3.17 and 2.65 mg/L, respectively) (136). Large (n=16,616), cross-sectional data from NHANES III demonstrated that obesity in men and women (20 years and older) was associated with increased CRP. Obese women in particular were 4.76 times more likely to have clinically raised CRP levels (>1.0 mg/dL) compared with their normal-weight counterparts (141). This association is likely driven by excess adiposity (142), as CRP is considered an indirect measure of total body fat, lipid, and apolipoprotein levels (140).

Encouragingly, weight loss in individuals who are overweight or obese decreases circulating levels of CRP (143). In one study, overweight women who lost weight, regardless of modality (i.e. diet, diet and aerobic exercise, or diet and resistance training), experienced a clinically significant decrease CRP levels from 3.1 mg/L to 2.89 mg/L (144). Additionally, in a sample of 450 obese adults, CRP levels declined from 8.8 mg/dL to 5.3 and 4.2 mg/dL through diet and exercise, or diet alone, after an 18 months of intervention (138). Thus, weight loss can help reduce circulating CRP levels, which may be particularly important for managing subclinical inflammation in the older, obese adult.

Recommendations for Intentional Weight Loss Remains Controversial Among Older Adults

Intentional weight loss is recommended to improve a variety of health outcomes in younger and middle-aged adults who are overweight or obese. However, older adults cannot be treated the same as younger and middle-aged adults because the causes of

mortality and the health impacts placed on these age groups are different (145). As a result, clinicians are more hesitant to prescribe weight loss for older adults because of the risks associated with weight loss and because observational evidence suggesting that weight loss may actually increase mortality in older adults (146,147). However, observational studies cannot definitively distinguish between intentional or unintentional (*i.e.* weight loss from disease onset) weight loss, prompting the need for examination of the risks and benefits of weight loss in the context of an RCT.

Several review articles have explored the risk:benefit ratio of weight loss in advance age by summarizing evidence across RCTs of intentional weight loss in older adults (16,148–150). The general consensus from these reviews is that intentional weight loss has its pros and cons in older adults, but the jury is still out as to whether the benefits outweigh the barriers due to the heterogeneity of the data that is of low to moderate quality and the lack of long-term follow up data. Of the studies currently conducted, most do suggest an immediate benefit of intentional weight loss on weight loss and fat mass, while also, more importantly, improving other measures such as physical function (16,148–150), a measure that might be a useful in motivating older adults to lose weight. Intentional weight loss in this population also reduces several clinical outcomes associated with being overweight or obese such as osteoarthritis (16), heart disease (16,149), diabetes (16), and improved quality of life (150), as well as some metabolic and inflammatory markers like IL-6 (148,149). Despite the positive impacts, some negative findings have been reported including loss of fat free mass and decrease in bone mineral density, which may increase the risk of fracture or sarcopenia. These losses were, however, partially mitigated by exercise, more specifically resistance exercise

(16,149,150), suggesting there is a way to reduce the negative effect of weight loss in this age group. Only one review assessed the long term maintenance of weight loss and found one feasibility study that showed that changes associated with weight loss and weight loss itself are feasible over a long period of time without contact from the study (149). Consequently, current data suggest intentional weight-loss therapy improves numerous aspects of health in obese older adults. Thus, weight-loss programs that minimize muscle and bone losses are recommended for obese older adults as well as those with functional impairments or medical complications (152).

Mortality is arguably the most important clinical endpoint of interest. However, few studies present data on weight loss and mortality in older adults (+65 years), contrary to the several publications looking at long term effects of weight loss in middle-aged individuals on mortality. In examining existing data on long-term risks or benefits of weight loss, one meta-analysis aimed to identify the impact of weight loss on mortality in individuals who were not severely obese and who did not have comorbidities in 26 prospective cohort studies. Authors calculated risk of mortality using adjusted data and stratified based on moderator variables such as intentional vs. unintentional weight loss or baseline health status (health vs. unhealthy). Analysis revealed unintentional weight loss increased the risk of mortality in both healthy and unhealthy (i.e. diabetes or obesity-related diseases) individuals, suggesting potential underlying disease. Similarly, self-reported intentional weight loss in healthy individuals may be at an increased risk of mortality by 11% (CI: 1.00-1.22), while it decreased the risk of mortality by 13% in the unhealthy individuals. Calculated together intentional weight loss in healthy and unhealthy individuals did not increase or decrease the risk of mortality (153). Although

these results may suggest healthy obese individuals should not lose weight, these results should not be considered conclusive due to the observational nature of the studies included. In order to more definitively determine the impacts of weight loss in older adults, investigators need to look at RCTs.

A meta-analysis sought to extend prior findings by examining long term mortality among middle-aged and older adults randomized to intentional weight loss interventions. Fifteen studies were included and all were ≥18-months duration, with participants randomized into either intentional weight loss or non-weight loss arms, and number of deaths in each treatment arm reported. In total, data from 17,186 obese individuals (BMI 30-46 kg/m^2) were included, with an average age of 52 years at baseline. Collectively, weight loss arms lost an average of 5.5 kg, with 264 deaths in the weight loss groups and 310 deaths in the non-weight loss groups. Investigators calculated relative risk of mortality based on available data, which indicated a 15% reduction in mortality in the intentional weight loss groups (154). These findings have recently been confirmed in another meta-analysis of weight loss RCTs and found an 18% reduction in mortality through intentional weight loss (155). Thus, prescribing intentional weight loss in middle-aged and potentially older adults appears to offer a mortality benefit, yet mechanisms underlying these improvements is unclear.

Purpose of this Thesis

Based on the epidemiologic evidence linking select physiologic variables to mortality, and meta-analytic data showing a reduction in mortality associated with

intentional weight loss, we aim to determine the impact intentional weight loss on the HAI composite score, component variables, and other candidate mortality biomarkers in the context of a six month intentional weight loss intervention conducted in older adults with obesity. We hypothesize participants randomized to the intentional weight loss intervention will experience improvements in HAI score and component variables as compared to participants randomized to weight stability, with the degree of weight loss directly correlated with such improvements.

METHODS

Study Design and Participants

This analysis utilizes data from The Medifast® for Seniors Study (NCT02730988), a six month RCT conducted at Wake Forest University, aimed at comparing the effects of weight loss (WL) versus weight stability (WS) on mobility and body composition in 96 older adults (54-79 years) with obesity (30-40 kg/m^2). The present thesis reports a secondary analysis, aimed at determining the impact of intentional WL on select mortality biomarkers. This study was approved by the Wake Forest School of Medicine Institutional Review Board, and all participants provided written and informed consent prior to enrollment.

Older men and women with obesity were recruited by promotional postcards via direct mailing in and around Forsyth County, NC for potential participation in this study. Specific inclusion and exclusion criteria can be found in **Table II**. General inclusion criteria comprised: age between 65-79 years, BMI between 30-40 kg/m^2, self-reported mobility limitation (difficulty walking ¼ mile or climbing stairs/performing house/yard work), sedentary lifestyle, non-smoking (<1 cigarette/day or 4/week within the year), weight stability (<5% weight change in the past 6 months), not dependent on a cane or walker, and willing to follow the dietary protocol. Participants were excluded if they had comorbidities for which the intervention was contraindicated.

Table II: Inclusion and Exclusion Criteria

Inclusion Criteria	**Exclusion Criteria**
Age 65-79 years	Weight loss or gain (±5%) in past 6 months
BMI = 30-40 kg/m^2	Prior bariatric surgery
Confirmation of self-reported mobility limitation, as assessed by phone screen/clinical staff	Multiple food allergies
Self-reported sedentary behavior	Difficulty with hearing/vision that interferes with study participation
Non-impaired cognitive function (MoCA>18)	Excessive alcohol use (>14 drinks/wk)
Stability of residence for next 2 years	Smoker (>1 cigarette/d within year)
Willing and able to follow dietary protocol	Insulin-dependent or uncontrolled diabetes (FBG>140 mg/dl)
Willing to provide informed consent	Uncontrolled hypertension (BP>160/100 mmHg)
Approved for participation by study physician	Abnormal kidney tests (GFR<40, creatinine>2.0)
Not involved in another behavioral or interventional research study	Regular use of medications that may influence body weight or composition
Able to provide own transportation to study visits and intervention	Severe systemic disease (diagnosis of Parkinson's disease, chronic liver disease, systemic rheumatic condition, gout, thyroid disease, end stage renal disease) or other systemic diseases/abnormal laboratory values which would preclude participants from safely participating in the protocol or impair the ability to complete the study
Not dependent on a cane or walker	Severe symptomatic heart disease or cardiovascular procedure within the past 3 months or history/current diagnosis/signs and symptoms of heart failure, with either reduced or preserved Left Ventricular ejection fraction
No evidence of clinical depression, eating disorder, or other contraindications for participation in voluntary weight loss	Cancer requiring treatment in past year, except skin cancer
English literacy	Judged unsuitable for the trial for any reason by clinical staff

Interventions

Dietary Weight Loss Intervention

Participants randomized to the WL program underwent a high protein dietary weight loss intervention, targeting 10% baseline weight. The Medifast® 4 & 2 & 1 Plan® was used to achieve a caloric deficit by providing 1100-1300 calories per day. This plan consisted of 4 meal replacement products (MRPs), 2 lean and green meals, and 1 healthy snack. MRP consisted of ~90-110 kcals, 11-15 g protein (primarily soy or dairy-based sources), and were fortified to ensure adequate micronutrient composition. Participants prepared 2 lean and green meals, which contained 5-7 oz. of lean protein, 3 servings of non-starchy vegetables, and up to 2 healthy fat servings. The snack consisted of 1 serving of fruit, dairy, or grain.

A Registered Dietitian (RD) lead 12 bi-weekly behavioral group counseling sessions to monitor weight loss, encourage consumption of only items approved as part of the weight loss plan, and discuss topics pertinent to weight control (including: self-monitoring, portion control, mindful eating, and overcoming weight loss barriers). Participants were encouraged to maintain baseline physical activity levels and complete daily food logs, which were reviewed bi-weekly to verify diet compliance.

Weight Stable Intervention

Participants randomized to the WS program attended 12 bi-weekly group behavioral education sessions, monitored by study staff to ensure weight stability (within ±5% of baseline) throughout study duration. Topics covered included: What is Successful Aging?, Preventing and Delaying Disease and Dysfunction, Managing Medications

Effectively, and Talking Effectively with your Healthcare Provider. If WS participants attended 75% (9 of 12) of the educational sessions, all baseline and follow-up testing sessions, and maintained weight stability (within ±5% of baseline) throughout the study, they were eligible to receive up to 3 months of Medifast® MRPs along with a 60 minute RD-lead dietary instructional session on how to follow the Medifast® 4 & 2 & 1 Plan® at the end of the study. As with the WL group, WS participants were encouraged to maintain baseline levels of physical activity for the duration of the intervention.

Measurements

Baseline Descriptive Characteristics

Demographic characteristics, including age, gender, and ethnicity were captured via self-report at baseline. Height was taken to the nearest 0.25 inches using a QuickMedical 235 Heightronic Digital Sadiometer (Issaquah, WA) and body mass was measured without shoes and outer garments to the nearest 0.1 kg on a calibrated certified electronic scale (Cardinal Detecto 758C, Webb City, MO) at baseline and follow-up visits. BMI was calculated as body mass in kilograms divided by height in meters squared.

Body Weight

Weight was taken without shoes and outer garments using a calibrated scale (Cardinal Detecto 758C, Webb City, MO). Measurements taken at the first intervention visit (immediately before randomization assignment) and last intervention visit were used to determine total amount of weight lost as a result of the intervention. Weight was also collected bi-weekly using a Health o meter® Professional 349KLX Digital Floor Medical

Scale (Pelstar LLC, McCook, IL) to track weight loss within the WL group and to ensure the WS group was remaining within <5% of baseline weight.

Healthy Aging Index Composite Score and Component Variables

As previously described (23), the HAI component variables include SBP, FVC, creatinine, FBG, and the MMSE. All measurements, except the MMSE, were taken at baseline (3-8 weeks prior to intervention start) and at the six month follow-up visit by trained research staff. The MoCA was utilized in place of the MMSE. Both MMSE and MoCA are quick screening tools for mild cognitive impairment, but the MoCA has demonstrated slight superior sensitivity and specificity for mild cognitive impairment and Alzheimer's disease (28,29).

SBP was assessed following a standard protocol [in which participants were seated for 5-10 minutes in a quiet room without distraction (156)] using an automatic blood pressure monitor (Dinamap Pro 100-V2, GE Medical Systems, Tampa, FL 33614). FVC was measured in liters according to the American Thoracic Society/European Respiratory Society (ATS/ERS) using an EasyOne spirometer (nnd Medical Technologies Inc., Andover, MA) (157). Serum creatinine and FBG (as part of a comprehensive metabolic panel) were collected after a 12 hour fast by trained study staff and analyzed at a clinical laboratory (LabCorp) using a standardized methodology, with concentration of both expressed in mg/dL (158). The MoCA was administered and scored by a trained study staff member (score range: 0-30, with higher scores meaning better function) (28).

The HAI composite score was derived as previously described (23). Briefly, component variables were given a score of 0-2 by dividing results based on previously determined tertile cutpoints, with the exception of FBG, which was scored using clinical cutoffs, and the MoCA score, which was scored based on tertile cutpoints that corresponded to those of the MMSE (see **Table III**) (159). Total HAI composite score was calculated by summing the scores of the individual HAI component variables. Scores ranged from 0-10, with 0 being the healthiest and 10 being the unhealthiest (23).

Table III: HAI Component Variable Cutpoints for Tertile Assignment.

		0	**1**	**2**
SBP (mmHg)		<126	126-143	≥143
FVC (L)	Male	≥3.84	3.19-3.84	<3.19
	Female	≥2.61	2.14-2.61	<2.14
Creatinine (mg/dL)	Male	<1.1	1.1-1.3	≥1.3
	Female	<0.8	0.8-1.0	≥1.0
FBG (mg/dL)		<100	100-125	≥126
MoCA (0-30)*		≥22	17-21	<17

*Tertile cutpoints correspond to that of MMSE tertile cutpoints

Additional Candidate Mortality Biomarkers

Additional candidate mortality biomarkers include gait speed, grip strength, DSST, FEV_1, IL-6, CRP, and Cystatin-C. All measurements were taken at baseline (3-8 weeks prior to intervention start) and at the six month follow-up visit by trained research staff.

Gait speed was assessed over 400-meters. Participants walked as quickly as possible at a pace that could be maintained for 10 laps of a 40-meter course (20 meters out and 20 meters back) while being timed (160), with results expressed in m/s. Handgrip strength (kg) was measured using an isometric hand dynamometer (Jamar, Bolingbrook, IL), adjusted to fit the hand size of each participant. The maximum score of two trials was recorded, which were alternately performed on each hand, with at least 30 seconds between hands (161). The DSST is 90-second a cognitive test for visuoattentional psychomotor speed (range 0-90) that was administered by trained study staff (162–164). Like FVC, FEV_1 was measured according to the ATS/ERS using an EasyOne spirometer (nnd Medical Technologies Inc., Andover, MA) (157). IL-6 and Cystatin-C were analyzed after processing, where blood was divided into aliquots and plasma aliquots were stored at -70°C at the Wake Forest Pepper Center Specimen Repository until analyses were conducted. Using previously described methodology (165,166), high sensitivity IL-6, and Cystatin-C were analyzed using enzyme-linked immunosorbent assay (ELISA) methods (R&D Systems, Minneapolis, MN), and CRP was analyzed using an automated immunoanalyzer (Siemens Medical Solutions, Malvern, PA). Samples with a CV of >25% or >20% for IL-6 or CRP, respectively, were reanalyzed and the sample with the lowest CV was used.

Statistical Analysis

Baseline characteristics are summarized overall and by group using descriptive statistics. For HAI composite, component variables, and candidate mortality biomarkers, treatment-specific six month means and six month group changes are presented using analysis of covariance models with adjustment for baseline values of the outcome and

gender. Standardized effect size estimates are also presented, derived from baseline standard deviations. The association between weight change and HAI score/component score is also estimated using partial Pearson correlations, adjusted for treatment group assignment and gender. We assume a Type I error rate of 0.05 for all statistical comparisons, and analyses are conducted using SAS v9.4 (SAS Institute, Cary, NC).

RESULTS

Participant Characteristics

Characteristics of the study sample (n=96) are previously reported (167). Briefly, this study sample was mostly older (70.3±3.7 years), Caucasian (72%), and female (74%). The average baseline BMI was 35.4±3.3 kg/m^2. Demographic characteristics did not differ significantly between intervention groups (all p>0.05). A total of 14 individuals were lost during the intervention (WL: n=4, WS: n=10), providing a final count of 82 participants who returned for six month follow-up testing (85.4% retention), with final sample sizes ranging from 33 to 44, depending on the outcome measure (see **Figure 1**).

Baseline values for HAI score, component variables, and other candidate mortality biomarkers are presented by group in **Table IV**. Average HAI score was 3.2±1.6 points, and both groups presented as pre-hypertensive and pre-diabetic. Among other candidate biomarkers, FEV_1, CRP, and IL-6 values were slightly above normal range limits, while Cystatin-C concentrations were slightly lower than typically reported.

Figure 1: Study CONSORT diagram

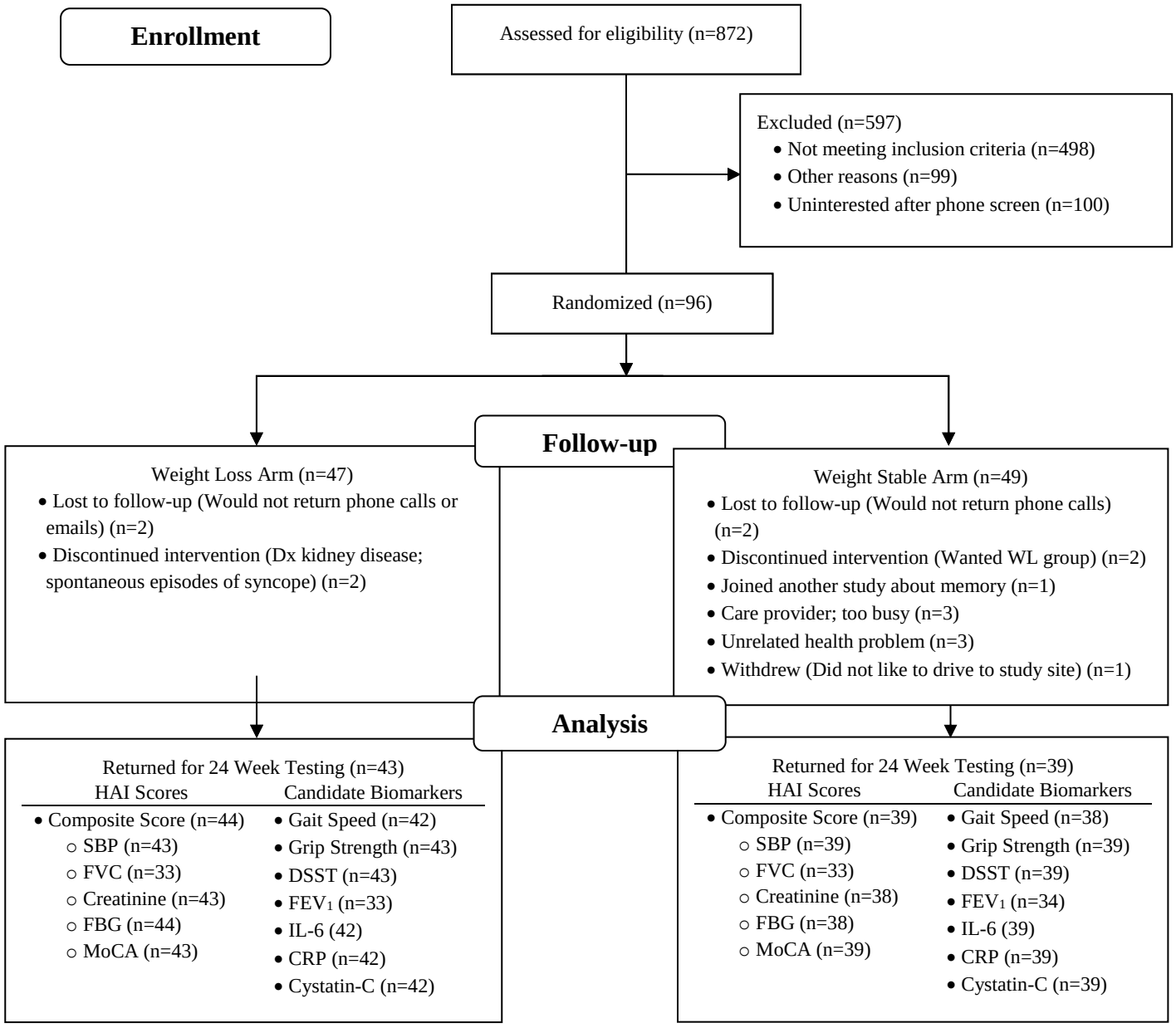


Table IV: Baseline HAI Composite Score, Component Variables, and Other Candidate Mortality Biomarkers by Weight Stable or Intentional Weight Loss Treatment Group.

Outcome Variable	Weight Stable		Weight Loss		Normal Reference Range
	n	**Mean ± SD**	***n***	**Mean ± SD**	
HAI (score, 0-10)	49	3.1 ± 1.6	47	3.2 ± 1.6	
SBP (mmHg)	49	133.1 ± 14.4	47	131.3 ± 16.0	90-120
FVC (L)	45	2.9 ± 0.8	41	2.9 ± 0.8	Median: 3.8
Creatinine (mg/dL)	48	0.9 ± 0.2	47	0.9 ± 0.2	<0.89
FBG (mg/dL)	48	105.1 ± 14.0	47	107.9 ± 18.3	<100
MoCA (0-30)	49	25.5 ± 2.8	47	25.7 ± 2.7	26-30
Candidate Mortality Biomarkers					
Gait Speed (m/s)	49	1.2 ± 0.2	47	1.2 ± 0.2	>0.8
Grip Strength (kg)	49	26.5 ± 8.9	47	26.0 ± 9.6	>21 women >37 men
DSST (score, 0-93)	49	55.9 ± 11.5	47	58.4 ± 10.9	>26
FEV_1 (L)	46	2.1 ± 0.6	41	2.1 ± 0.6	>70% predicted
Predicted FVC (%)	45	92.8 ± 19.3	41	92.0 ± 21.9	70-130
Predicted FEV_1 (%)	46	98.1 ± 13.6	41	98.0 ± 11.8	70-130
IL-6 (pg/mL)	49	3.8 ± 2.9	45	4.6 ± 6.2	<2.5
CRP (mg/L)	49	6.7 ± 5.9	45	9.2 ± 10.8	<1
Cystatin-C (ng/mL)	49	36.2 ± 10.9	45	36.3 ± 10.7	<1.03

Intervention Effects on Weight, HAI Composite Score, Component Variables, and Candidate Mortality Biomarkers.

WL participants lost an average of 8.85 (CI: -10.37, -7.34) kg over the six month period and weight remained stable in the WS group [-1.33 (-2.90, 0.25) kg; group*time $p<0.01$]. After the six month intervention, the WL group improved HAI composite score

by 0.63 points more compared to the WS group [WL: -0.80 (-1.18, -0.41) points vs WS: -0.17 (-0.57, 0.23) points]; *p*=0.02 (see **Table V**). Among the HAI component variables, FBG was significantly reduced [WL: -4.31 (-8.22, -0.40) mg/dL vs WS: 1.47 (-2.61, 5.55) mg/dL; $p = 0.03$] and FVC was marginally increased [WL: 0.11 (-0.02, 0.23) L vs WS: -0.04 (-0.17, 0.09) L; $p = 0.08$] in the WL group. Though not significant, SBP decreased twice as much in the WL group [-7.43 (-11.31, -3.55) mmHg] compared to WS group [-3.23 (-7.24, 0.77) mmHg], while creatinine levels and MoCA scores did not change from baseline in either group. Of the other candidate biomarkers, all variables tended to slightly improve or remain stable (versus worsening) in the weight loss group, except DSST, but the largest reduction was observed for Cystatin-C [WL: -2.57 (-4.41, -0.73) ng/mL vs WS: 0.10 (-1.79, 1.99) ng/mL; $p = 0.04$].

For comparison purposes, standardized intervention effects on all HAI composite score and component variables as well other candidate mortality biomarkers are presented in **Figures 2 and 3**. Graphical points represent the change per baseline SD and lines represent the 95% CI of the standardized change. After adjustment for baseline value and gender, the greatest significant intervention effect was observed for HAI composite score [WL: -0.47 (-0.71, -0.24) vs WS: -0.09 (-0.34, 0.15); *p*=0.02], followed by FBG [WL: -0.23 (-0.47, 0.01) vs WS: 0.13 (-0.12, 0.38); *p*=0.03], and Cystatin-C [WL: -0.21 (-0.38, -0.04) vs WS: 0.04 (-0.14, 0.21); *p*=0.04].

Table V: Intervention Effect of Intentional Weight Loss on Estimates of HAI Composite Score, Component Variables, and Other Candidate Mortality Biomarkers.

Outcome Variable	Weight Stable		Weight Loss		*p*-value
	6-Month Mean (95%CI)	6-Month Change (95%CI)	6-Month Mean (95%CI)	6-Month Change (95%CI)	
HAI (score, 0-10)	3.01 (2.61, 3.41)	-0.17 (-0.57, 0.23)	2.38 (2.00, 2.77)	-0.80 (-1.18, -0.41)	0.02
SBP (mmHg)	129.36 (125.36, 133.37)	-3.23 (-7.24, 0.77)	125.17 (121.29, 129.05)	-7.43 (-11.31, -3.55)	0.11
FVC (L)	2.84 (2.71, 2.96)	-0.04 (-0.17, 0.09)	2.98 (2.86, 3.11)	0.11 (-0.02, 0.23)	0.08
Creatinine (mg/dL)	0.88 (0.85, 0.91)	-0.02 (-0.05, 0.01)	0.87 (0.84, 0.90)	-0.02 (-0.05, 0.01)	0.80
FBG (mg/dL)	108.56 (104.47, 112.64)	1.47 (-2.61, 5.55)	102.77 (98.87, 106.68)	-4.31 (-8.22, -0.40)	0.03
MoCA (0-30)	25.80 (25.14, 26.46)	0.07 (-0.59, 0.73)	25.82 (25.18, 26.46)	0.09 (-0.55, 0.73)	0.97
Candidate Mortality Biomarkers					
Gait Speed (m/s)	1.14 (1.11, 1.17)	-0.03 (-0.06, 0.00)	1.17 (1.14, 1.20)	0.00 (-0.03, 0.04)	0.12
Grip Strength (kg)	25.91 (24.88, 26.94)	-0.30 (-1.33, 0.73)	26.79 (25.77, 27.81)	0.59 (-0.43, 1.61)	0.18
DSST (score, 0-93)	60.88 (59.28, 62.47)	3.34 (1.75, 4.93)	59.70 (58.16, 61.24)	2.16 (0.62, 3.71)	0.26
FEV_1 (L)	2.12 (2.06, 2.19)	0.01 (-0.05, 0.08)	2.16 (2.09, 2.22)	0.04 (-0.02, 0.11)	0.46
Log IL-6 (log-pg/mL)	1.27 (1.13, 1.40)	0.14 (-0.00, 0.27)	1.16 (1.03, 1.30)	0.03 (-0.10, 0.17)	0.27
Log CRP (log-mg/L)	1.46 (1.21, 1.71)	0.05 (-0.20, 0.30)	1.32 (1.08, 1.56)	-0.09 (-0.33, 0.15)	0.39
Cystatin-C (ng/mL)	36.66 (34.77, 38.55)	0.10 (-1.79, 1.99)	33.99 (32.15, 35.83)	-2.57 (-4.41, -0.73)	0.04

Figure 2: Forest Plot of Standardized Intervention Effect Estimates of Intentional Weight Loss on HAI Composite Score and Component Variables.

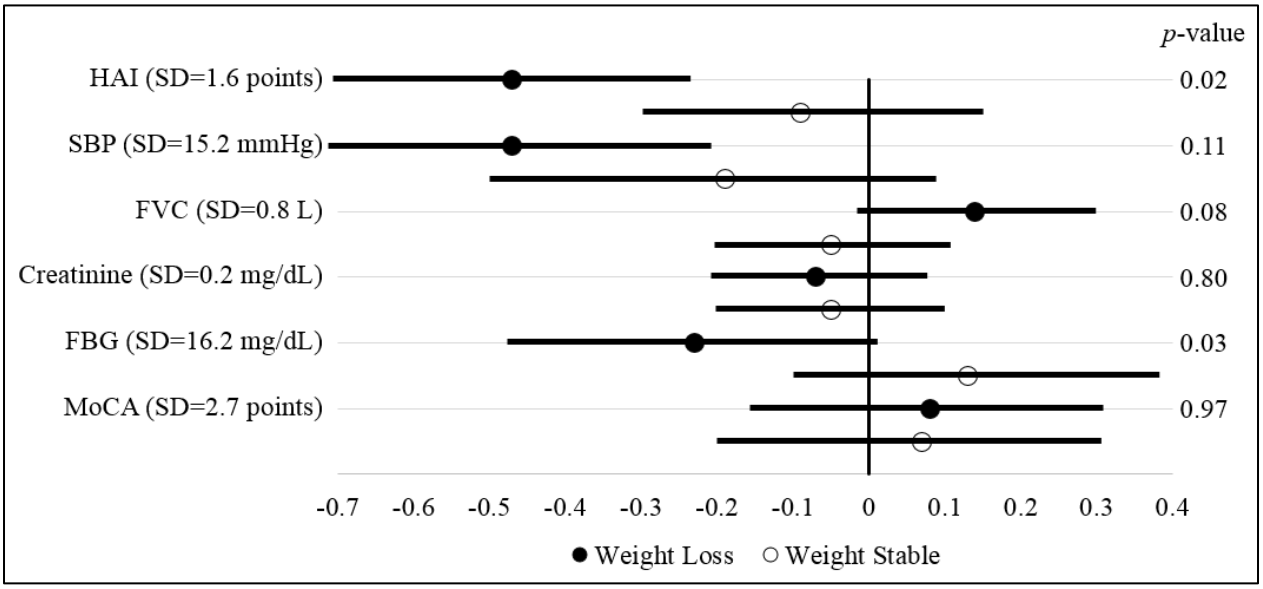
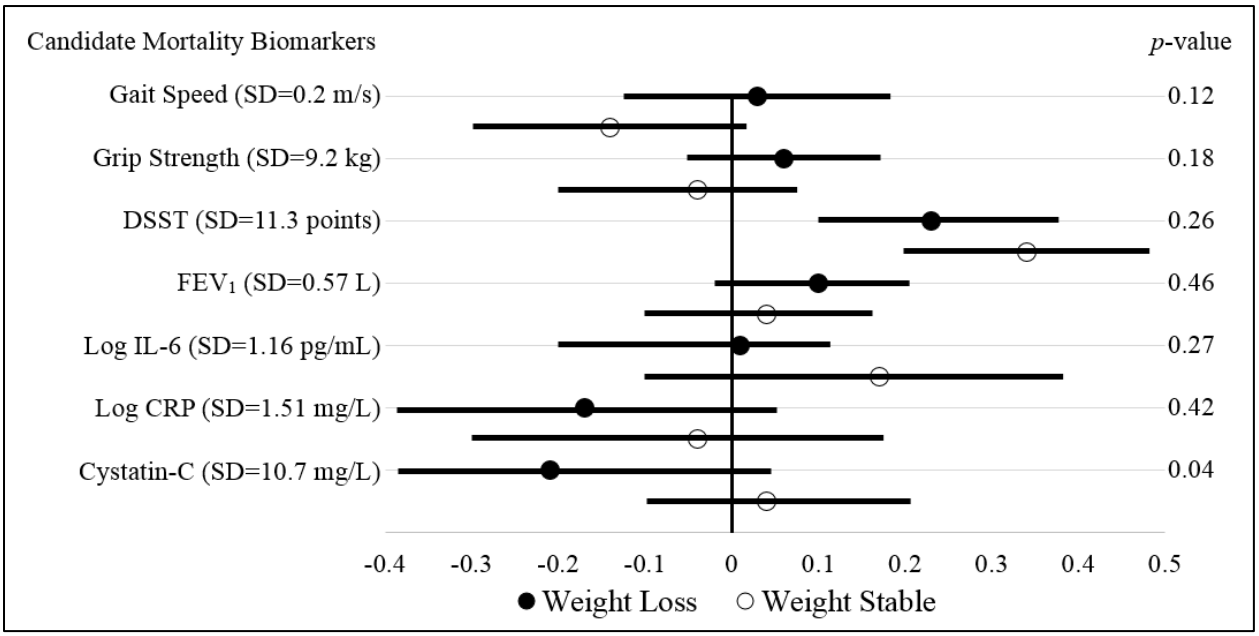


Figure 3: Forest Plot of Standardized Intervention Effect Estimates of Intentional Weight Loss on Candidate Mortality Biomarkers.



Associations Between Weight Change and Change in the HAI Composite Score, Component Variables, and Other Candidate Mortality Biomarkers

Correlations and model-adjusted associations between changes in weight and all outcome measures can be found in **Table VI**. With every one kg of weight lost, HAI score decreased by 0.07 (0.03, 0.12) points (p<0.01), driven by a 0.82 (0.27, 1.37) mmHg reduction in SBP and 0.02 (-0.04, -0.01) L increase in FVC (both p<0.01). Among other candidate mortality biomarkers, change in gait speed, and FEV_1 were negatively correlated with weight change, while Cystatin-C was positively associated with weight change (all p<0.01).

Table VI: Associations Between Weight Change and Change in HAI Composite Score, Component Variables, and Candidate Mortality Biomarkers.

Outcome Variable	**r**	***p*-value**	**β (95%CI)**	***p*-value**
HAI (score, 0-10)	0.35	<0.01	0.07 (0.03, 0.12)	<0.01
SBP (mmHg)	0.33	<0.01	0.82 (0.27, 1.37)	<0.01
FVC (L)	-0.41	<0.01	-0.02 (-0.04, -0.01)	<0.01
Creatinine (mg/dL)	-0.03	0.76	-0.00 (-0.01, 0.00)	0.62
FBG (mg/dL)	0.21	0.06	0.40 (-0.08, 0.87)	0.10
MoCA (score, 0-30)	-0.04	0.72	-0.02 (-0.10, 0.06)	0.62
Candidate Mortality Biomarkers				
Gait Speed (m/s)	-0.30	<0.01	-0.00 (-0.01, -0.00)	0.01
Grip Strength (kg)	-0.11	0.32	-0.07 (-0.18, 0.04)	0.22
DSST (score, 0-93)	0.04	0.71	0.06 (-0.12, 0.24)	0.50
FEV_1 (L)	-0.43	<0.01	-0.01 (-0.02, -0.00)	<0.01
Log IL-6 (log-pg/mL)	0.02	0.85	0.00 (-0.01, 0.02)	0.65
Log CRP (log-mg/L)	0.02	0.89	0.00 (-0.03, 0.03)	0.79
Cystatin-C (ng/mL)	0.32	<0.01	0.32 (0.09, 0.55)	<0.01

DISCUSSION

As hypothesized, findings from this analysis utilizing data from a six month RCT of weight loss and weight stability in older adults with obesity demonstrated intentional weight loss improved HAI composite score, with the degree of reduction positively associated with the amount of weight lost. Component variables showing the largest changes were FBG, FVC, and SBP, as the greatest standardized intervention effects were observed for these biomarkers. Of other candidate mortality biomarkers, Cystatin-C (-2.57 ng/mL), a traditional marker of kidney function, showed an effect large enough to be nominally statistically significant. Collectively, our findings suggest that intentional WL reduces mortality risk, largely through metabolic and pulmonary improvement, and point to Cystatin-C as a potential target to evaluate the success of mortality reducing interventions.

Findings presented here confirm and extend prior work. Previously, meta-analysis findings suggest intentional weight loss in adults with obesity reduces mortality risk by 15-18% (154,155). Our observation that a six month weight loss intervention yields a net reduction in the HAI of 0.63 points translates into an approximate 11% mortality risk reduction, which is slightly reduced, but consistent with these findings. Our results further contribute to the literature providing evidence for speculation regarding potential mechanisms underlying the weight loss associated mortality advantage.

Changes in component variables in the present analysis are supported by previous literature. Reductions in FBG and SBP are both well-established outcomes of intentional WL (81,82,168). Changes in FBG in the present analysis are slightly lower than that of meta-analytic data in real-world settings (82), but slight inconsistencies are likely due to

the modest sample size, short duration of the present study, and differences in intervention type. Furthermore, though not statistically significant, changes in SBP in the present analysis are also considered clinically significant, as the WL group decreased SBP by 7.43 mmHg, which is more than double that of the WS group (-3.23 mmHg). Additionally, MoCA scores remained stable in both groups, which aligns with limited data concerning response of MoCA scores and general cognitive function to WL, with equivocal findings reported (97,98).

However, the relationship between WL and pulmonary and kidney function has rarely been studied. Increases in fat mass are associated with decreases in FEV_1 and FVC values (50). RCTs examining the weight loss and lung function relationship, however, are few. The limited evidence supports improvements in function after a period of weight loss (52), but conventional respiratory function test (*i.e.* FVC and FEV_1) modifications are typically less dramatic with WL in obese compared to extreme obese individuals, with changes likely due to decreased restrictive load, decreased demand for ventilation, and improved muscle efficiency with WL (169). This previous literature supports and explains the marginal, but not significant increase in FVC in the present analysis.

Kidney function estimates are typically reported as glomerular filtration rate (GFR), calculated using creatinine or Cystatin-C. Equations using creatinine are limited due to the impact of muscle mass and diet on creatinine, producing inconsistent results (170). Some studies demonstrate improvements in kidney function using creatinine with WL (66), while other studies show a decrease in kidney function (171); thus, stability of creatinine in the present study is not surprising due to inconclusive evidence regarding WL and creatinine levels. However, the significant Cystatin-C reduction observed in the

present analysis is supported by previous findings, as estimates of kidney function via Cystatin-C are slightly superior due to the independence of Cystatin-C from height, gender, age, and muscle mass. Adipose tissue is also thought to produce Cystatin-C (172), which could further explain the significant reduction observed through weight loss in this analysis, though studies confirming this notion are few.

Both IL-6 and CRP are known to be associated with obesity (135) and improve with WL (102,134,139). Results of the present study did not demonstrate a significant six month difference for these variables, but both remained fairly constant instead of worsening in the weight loss group. Likely the discrepancy between previous literature and the present study is due to the short duration of the present study, compared to the 18 month duration in previous literature, suggesting that changes in these inflammatory markers take longer to respond to WL. The diet consumed by participants in the present study may also have been pro-inflammatory, potentially neutralizing any reduction of these inflammatory biomarkers from weight loss.

To our knowledge, this is the first trial of intentional weight loss to examine the HAI. Strengths of the study design include a weight stable control group, and excellent measures of protocol compliance. Weaknesses include the modest sample size and short study duration, not providing enough power or time fully to evaluate changes in measures that are more variable within individuals or slower to respond to weight loss. Due to the exploratory nature of our analysis, we did not adjust for multiple comparisons, and due to the number of outcome variables assessed, the *p*-values should be interpreted with caution. Lastly, we assumed a linear relationship between weight change in HAI, but the true association may not be linear, limiting the impact of these results.

In conclusion, we report that intentional WL may reduce mortality risk through metabolic and pulmonary factors captured by the HAI. To our knowledge, this is the first study to examine the responsiveness of the HAI composite score, component variables, and other potential biomarkers to intentional weight loss in older adults with obesity, contributing to the current literature by suggesting potential mechanisms behind mortality reduction through WL. Future studies might replace Cystatin-C with creatinine in the HAI as a kidney function measure with increased potential to observe index score improvements. Larger scale studies of longer duration are needed to confirm these results so findings can be used to create more targeted interventions for, or to evaluate interventions aimed at, mortality risk reduction.

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Curriculum Vitae
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EDUCATION:

2018	MS	Wake Forest University, Winston-Salem, NC Candidate for Master of Science in Health and Exercise Science College of Arts and Sciences Thesis: Effect of Intentional Weight Loss on Mortality Biomarkers in Older Adults with Obesity.
2016	BS	Elon University, Elon, NC Bachelor of Science in Exercise Science, Minor in Public Health College of Arts and Sciences

RESEARCH EXPERIENCE:

2016 – Present	Graduate Research Assistant, Medifast Study (NCT02730988) Research Advisor – Dr. Kristen Beavers, PhD
2017	Research Interventionist Assistant, Strength Training and Running Study (NCT02730988) Supervisor – Megan Jenkins, MS
2015-2016	Undergraduate Research Assistant, Resveratrol Research Research Advisors – Dr. Caroline Ketcham, PhD, Dr. Paul Miller, PhD, FACSM
2014-2016	Undergraduate Student Research Project, Effects of Drinking vs Rinsing with Water on Physiological and Affective Response During a 15-km Running Session. Research Advisor – Dr. Svetlana Nepocatych, PhD

CLINICAL EXPERIENCE:

2017-2018	New Member Coordinator Healthy Exercise and Lifestyle ProgramS (HELPS), Winston-Salem, NC Supervisor – Erika Janssen, MS
2016-2017	Graduate Student Intern HELPS, Winston-Salem, NC Supervisor – Erika Janssen, MS

TEACHING EXPERIENCE:

2016-Present	Graduate Teaching Assistant, Wake Forest University Introduction to Health and Exercise Science (HES 101) Supervisor – Sharon Woodard, MS
Spring 2016	Undergraduate Teaching Assistant, Elon University Exercise Testing and Prescription (ESS 424) Supervisor – Dr. Svetlana Nepocatych, PhD
Fall 2014	Undergraduate Teaching Assistant, Elon University Elon 101 (ELN 101) Supervisor – Dr. Svetlana Nepocatych, PhD
Spring 2014	Undergraduate Teaching Assistant, Elon University Anatomy Lab (BIO 263) Supervisor – Ann Marie Wilson

LAB EXPERIENCE:

Summer 2017	Integrative Biology Core Lab Technician Intern, WFU Health Science Gerontology Lab, Winston-Salem, NC Supervisor – Karin Murphy
2014-2016	Exercise Science Lab Manager Elon University Department of Exercise Science, Elon, NC Supervisors – Dr. Caroline Ketcham, PhD,

PUBLICATIONS AND PRESENTATIONS:

ABSTRACTS

Shaver LN, Beaver DP, Kritchevsky SB, and Beavers KM. The Effect of Intentional Weight Loss on Biomarkers of Mortality in Older Adults with Obesity. International Conference on Frailty & Sarcopenia Research Annual Meeting, Miami, FL. 03/02/2018.

Shaver LN, Hall EE, O'Neal EK, and Nepoctych N. Physiological and Perceptual Response of Drinking vs Mouth Rinsing with Water During a 15-km Running Time Trial. American College of Sports Medicine (ACSM) Annual Meeting, Boston, MA. 06/02/2016.

Nepocatych N, **Shaver LN**, Hall EE. The Influence of Drinking vs Rinsing with Water During Prolonged Running Exercise on Affective Response. ACSM Annual Meeting, Boston, MA. 06/02/2016.

POSTER PRESENTATIONS
The Effects of Intentional Weight Loss on the Healthy Aging Index in Older Adults with Obesity. Southeast ACSM Annual Meeting, Chattanooga, TN. 02/15/2018; and Aging Re-Imagined DEAC Talks & Posters, Winston-Salem, NC. 05/03-04/2018.

Effects of Drinking vs Rinsing with Water on Physiologic and Affective Response During a 15-km Running Session. Summer Undergraduate Research Experience, Elon, NC. 07/24/2015; and Southeast ACSM Annual Meeting, Greenville, SC. 02/18/2016.

Physiological and Perceptual Response of Drinking vs Mouth Rinsing with Water During a 15-km Running Time Trial. ACSM Annual Meeting, Boston, MA. 06/02/2016.

ORAL PRESENTATIONS
The Effect of Intentional Weight Loss on Biomarkers of Mortality in Older Adults with Obesity. International Conference of Frailty & Sarcopenia Research Annual Meeting, Miami, FL. 03/02/2018.

Effects of Drinking vs Rinsing with Water on Physiological and Affective Response During a 15-km Running Session. Spring University Research Forum, Elon, NC. 04/26/2016.

COMMUNITY WORKSHOPS
National Physical Activity/Exercise Recommendations and Resources to Meet Those Recommendations. Cooperative Baptist Fellowship of North Carolina Annual Meeting, Winston-Salem, NC. 03/16/2018.

CERTIFICATIONS:

2016-Present	CPR/AED Certified
2017-Present	ACSM Certified Clinical Exercise Physiologist

HONORS AND AWARDS:

Summer 2015	Summer Undergraduate Research Experience Recipient Elon University
February 2016	Undergraduate Poster Award Nominee Southeast ACSM Annual Meeting, Greenville, SC
2016-2018	Wake Forest Graduate School Full Tuition Scholarship Wake Forest University Health and Exercise Science Department
2018	3 Minute Thesis Award Winner Wake Forest Graduate School and Postdoc Research Day

PROFESSIONAL AFFILIATION:

2015-Present	American College of Sports Medicine Member