Research Article

Effect of Intentional Weight Loss on Mortality Biomarkers in Older Adults With Obesity

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Abstract

Background: Observational research has identified several mortality biomarkers; however, their responsiveness to change is unknown. We tested whether the Healthy Aging Index (HAI) and other mortality biomarkers were responsive to intentional weight loss (WL), which is associated with lower mortality risk in recent meta-analyses.

Methods: Older adults (70.3 ± 3.7 years) with obesity were randomized into a 6-month WL ($n = 47$) or weight stability (WS: $\pm 5\%$ baseline weight; $n = 48$) program. Baseline and 6-month HAI score (0–10) was calculated from component sum (each 0–2: systolic blood pressure, forced vital capacity [FVC], creatinine, fasting blood glucose [FBG], Montreal Cognitive Assessment), and gait speed, grip strength, Digit Symbol Substitution Test, FEV₁, Interleukin-6, C-Reactive Protein, and Cystatin-C were assessed at baseline and 6 months.

Results: Mean baseline HAI was 3.2 ± 1.6 . By 6 months, WL participants lost 8.87 (95% CI: $-10.40, -7.34$) kg, whereas WS participants remained weight stable. WL group reduced HAI score (WL: -0.75 [95% CI: $-1.11, -0.39$] vs WS: -0.22 [95% CI: $-0.60, 0.15$]; $p = .04$), and components changing the most were FBG (WL: -3.89 [95% CI: $-7.78, 0.00$] mg/dL vs WS: 1.45 [95% CI: $-2.61, 5.50$] mg/dL; $p = .047$) and FVC (WL: 0.11 [95% CI: $-0.01, 0.23$] L vs WS: -0.05 [95% CI: $-0.17, 0.08$] L; $p = .06$). Among other biomarkers, only Cystatin-C significantly changed (WL: -2.53 [95% CI: $-4.38, -0.68$] ng/mL vs WS: 0.07 [95% CI: $-1.85, 1.98$] ng/mL; $p = .04$). Combining treatment groups, 1 kg WL was associated with a 0.07 (95% CI: $0.03, 0.12$) HAI reduction ($p < .01$).

Conclusion: Intentional WL via caloric restriction reduced HAI score by 0.53 points, largely attributable to metabolic and pulmonary improvements.

Keywords: Healthy Aging Index, Successful Aging, Multimorbidity, Longevity

Increasing knowledge of aging biology has identified interventions that extend health and life span in laboratory animal studies (1). For example, macro-caloric restriction (while maintaining necessary micro-calorie intake) consistently slows the rate of aging in animal models, with a 40% caloric reduction increasing life span by 30%–40% in many mammalian species (2). Meta-analyses of weight loss (WL) randomized controlled trials (RCTs) suggest that caloric restriction modestly extends human life span as well, with a 15%–18% reduction in all-cause mortality risk observed in participants assigned to caloric restriction compared to noncaloric

restriction interventions (3,4). Thus, caloric restriction in humans might be used to evaluate potential biomarker responsiveness for use in testing other kinds of interventions targeting aging biology. In support of this concept, recent results from the CALERIE study (5) suggest a 10% caloric restriction achieved and maintained over a 2-year period affected some (ie, TNF- α and hsCRP), but not all (ie, IL-6, IL-8, MCP-1), potential modulators of longevity induced by caloric restriction in animal models (6).

Epidemiologic investigations have identified several physiologic biomarkers of multiple organ systems which reliably predict

mortality risk. Building on prior work (7,8), in 2014, Sanders et al. used a compilation of biomarkers (including: systolic blood pressure [SBP], forced vital capacity [FVC], serum creatinine, fasting blood glucose [FBG], and a cognitive function measure [Modified Mini-Mental Status Examination; 3MS]) to derive a “Healthy Aging Index” (HAI) score (range: 0–10), and determine its association with mortality risk within the Cardiovascular Health Study (9). A HAI score of 7–10 was associated with 2.6-fold increased mortality risk compared to those with a score of 0–2, with mortality risk increasing by 17% per HAI unit increase after adjustment for age and other risk factors. Since this publication, the HAI has been further associated with mortality (9–12)—even in the absence of clinically diagnosed disease (10,12)—as well as cardiovascular disease (11), disability (8), and candidate genes associated with a healthy aging phenotype (13,14).

To date, the HAI has been used as a predictor of future events, but not as an outcome for interventions targeting mortality risk. Due to robust data linking WL with mortality risk reduction in animal and human models, as well as HAI with mortality, we sought to determine the impact of intentional WL on the HAI (and its components) using data collected as part of a previously published 6-month WL intervention in older adults with obesity (15). We hypothesized that individuals assigned to WL would experience improvements in HAI score compared to weight stable (WS) individuals. We further sought to determine whether the degree of WL directly correlated with the degree of HAI improvement. Lastly, in exploratory analyses, we examined the impact of WL on several candidate mortality biomarkers (including: gait speed, grip strength, Digit Symbol Substitution Test [DSST], forced expiratory volume in 1 second [FEV₁], high-sensitivity interleukin-6 [hsIL-6], high-sensitivity C-reactive protein [hsCRP], and Cystatin-C), selected due to their known associations with mortality (16–20).

Methods

Study Design and Participants

This analysis utilizes data from The Medifast for Seniors Study (NCT02730988), a 6-month RCT conducted at Wake Forest University recruiting from September 18, 2015 to September 14, 2016, aimed at comparing the effects of WL versus WS on mobility and body composition in 96 older adults (54–79 years) with obesity (30–40 kg/m²). 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. Specific study design including inclusion and exclusion criteria are reported in a separate publication (15). The present manuscript reports a secondary analysis, aimed at determining the impact of intentional WL on possible mortality biomarkers.

Interventions

Dietary WL intervention

Participants randomized to the WL program underwent a high protein dietary WL intervention, targeting 10% baseline WL. The Medifast® 48&2&1 Plan® was used to achieve a caloric deficit by providing 1,100–1,300 calories per day through four meal replacement products (90–110 kcals, 11–15 g protein), two lean and green meals (each 5–7 oz. lean protein, three servings of non-starchy vegetable, and up to two healthy fat servings), and one healthy snack (fruit, dairy, or grain). A Registered Dietitian led 12 bi-weekly behavioral group counseling sessions to monitor WL, encourage consumption of only WL plan approved items, and discuss topics pertinent to

weight control. Participants were encouraged to maintain baseline physical activity levels and complete daily food logs, which were reviewed bi-weekly to verify diet compliance.

WS Intervention

Participants randomized to the WS program attended 12 bi-weekly group behavioral education sessions, monitored by study staff to ensure WS (within $\pm 5\%$ of baseline) throughout the study duration. WS participants were encouraged to maintain baseline dietary habits and baseline levels of physical activity for the duration of the intervention.

Measurements

Baseline descriptive characteristics

Demographic characteristics, including age, sex, and ethnicity, were assessed by participant report at baseline. Height was taken to the nearest 0.1 cm using a QuickMedical 235 Heightronic Digital Stadiometer (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. Body mass index was calculated as body mass in kilograms divided by height in meters squared.

HAI score and component variables

As previously described (9), the HAI component variables include SBP, FVC, creatinine, FBG, and the 3MS. All measurements, except the 3MS, were taken at baseline (3–8 weeks prior to intervention start) and at the 6-month follow-up visit by trained research staff. The Montreal Cognitive Assessment (MoCA) tool was utilized in place of the 3MS. Though studies comparing the 3MS and MoCA are few, both are test for mild cognitive impairment and demonstrate superior sensitivity and specificity compared to the Mini-Mental Status Examination from which the 3MS was derived (21–23).

SBP was assessed following a standard protocol (after 5–10 minutes seated in a quiet room without distraction (24)) 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) (25). Standardized serum creatinine and FBG analyses (as part of a comprehensive metabolic panel) were conducted by a clinical laboratory (LabCorp), with concentration of both expressed in mg/dL (26). The MoCA was administered and scored by a trained study staff member (score range: 0–30, with higher scores meaning better function) (23).

The HAI score was derived as previously described (9), with some modification to accommodate missing spirometry data (see below). Components were given a score 0–2 by dividing results based on previously reported tertile cutpoints (see [Supplementary Table 1](#)), with the exception of FBG, which was scored using clinical cutoffs, and the MoCA score, which was scored based on tertile cutpoints corresponding to those of the 3MS (27). SBP and FBG component scores were assigned based on measured physiologic values, regardless of medication use. Total HAI score was calculated by summing the scores of the individual HAI components. Scores ranged from 0 to 10, with 0 being the healthiest and 10 being the unhealthiest (9). For participants with missing FVC ($n = 16$), we summed the four available component scores as described and multiplied the sum by 1.25 so the final HAI scores ranged from 0 to 10.

Additional Candidate Mortality Biomarkers

Additional candidate mortality biomarkers include gait speed, grip strength, DSST, FEV₁, hsIL-6, hsCRP, and Cystatin-C. All measurements were taken at baseline (3–8 weeks prior to intervention start) and at the 6-month follow-up visit by trained research staff.

Gait speed was assessed over 400 m (10 laps of a 40-m course) (28), 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 for each hand (29). The DSST is a 90-second cognitive test for visuoattentional psychomotor speed (range 0–90) that was administered by trained study staff (30). FEV₁ was measured according to the ATS/ERS using an EasyOne spirometer (nnd Medical Technologies Inc., Andover, MA) (25). Using 12-hour fasting blood samples obtained and processed via previously described methodology (31,32), hsIL-6 and Cystatin-C were measured using enzyme-linked immunosorbent assay (ELISA) methods (R&D Systems, Minneapolis, MN), and hsCRP was analyzed using an automated immunoanalyzer (Siemens Medical Solutions, Malvern, PA). Inter- and intra-assay coefficient of variations were 7.8% and 7.4%, 6.0% and 4.8%, and 4.9% and 4.2% for hsIL-6, Cystatin-C, and hsCRP, respectively.

Statistical Analysis

Baseline characteristics are summarized overall and by group using descriptive statistics. For HAI score, component variables, and candidate mortality biomarkers, treatment-specific 6-month means and 6-month group changes are presented using analysis of covariance models with adjustment for baseline values of the outcome and sex. A sensitivity analysis was conducted including only individuals with complete HAI data (ie, nonmissing for all five component variables;

$n = 65$). Standardized effect size estimates are also presented, derived from baseline standard deviations. The association between weight change and HAI score and components are also estimated using partial Pearson correlations, adjusted for treatment group assignment and sex. Due to the exploratory nature of these analyses, no adjustments were made for multiple comparisons. 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

A total of 95 participants (of 96) presented with complete HAI data at baseline, with demographic and biomarker data summarized in Table 1. Overall, the study sample was older (70.3 ± 3.7 years), Caucasian (72%) and female (74%), with an average baseline body mass index of 35.3 ± 3.3 kg/m². Demographic characteristics did not differ significantly between intervention groups (all $p > .05$). Average HAI score was 3.2 ± 1.6 , and both groups presented as prehypertensive and prediabetic. Among other candidate biomarkers, hsCRP and hsIL-6 values were slightly above normal range limits. Eighty-one participants (WL: $n = 43$, WS: $n = 38$) returned for 6-month follow-up testing (85% retention) and had complete follow-up data on all HAI components, except FVC (missing $n = 16$; see Supplementary Figure 1). Demographic characteristics among participants lost to follow up did not significantly differ from those included in the final analyses ($p > .05$), although hsCRP was lower in those who completed the intervention versus those lost to follow up (7.2 ± 7.4 vs 12.7 ± 13.8 mg/L, respectively; $p = .03$).

Table 1. Baseline HAI Score, Its Components, and Other Candidate Mortality Biomarkers by Treatment Group in a 6-mo Weight Loss Study in Older Adults With Obesity

Outcome Variable	Weight Stable		Weight Loss	
	<i>n</i>	Mean $\pm$ SD	<i>N</i>	Mean $\pm$ SD
Age (years)	48	69.3 $\pm$ 3.1	47	71.4 $\pm$ 3.9
Female, <i>n</i> (%)	48	35 (72.9)	47	35 (74.5)
White, <i>n</i> (%)	48	35 (72.9)	47	33 (70.2)
Weight (kg)	48	97.8 $\pm$ 12.9	47	96.1 $\pm$ 16.8
BMI (kg/m ²)	48	35.5 $\pm$ 3.0	47	35.2 $\pm$ 3.5
HAI (score, 0–10)	48	3.2 $\pm$ 1.6	47	3.3 $\pm$ 1.6
SBP (mmHg)	48	133.5 $\pm$ 14.3	47	131.3 $\pm$ 16.0
FVC (L)	44	2.9 $\pm$ 0.8	41	2.9 $\pm$ 0.8
Creatinine (mg/dL)	48	0.9 $\pm$ 0.2	47	0.9 $\pm$ 0.2
FBG (mg/dL)	48	105.1 $\pm$ 14.0	47	107.9 $\pm$ 18.3
MoCA (0–30)	48	25.4 $\pm$ 2.8	47	25.7 $\pm$ 2.7
Candidate Mortality Biomarkers				
Gait Speed (m/s)	48	1.2 $\pm$ 0.2	47	1.2 $\pm$ 0.2
Grip Strength (kg)	48	26.6 $\pm$ 8.9	47	26.0 $\pm$ 9.6
DSST (score, 0–93)	48	55.7 $\pm$ 11.6	47	58.4 $\pm$ 10.9
FEV ₁ (L)	45	2.1 $\pm$ 0.6	41	2.1 $\pm$ 0.6
Predicted FVC (%)	44	92.8 $\pm$ 19.6	41	92.0 $\pm$ 21.9
Predicted FEV ₁ (%)	45	98.1 $\pm$ 13.8	41	98.0 $\pm$ 11.8
hsIL-6 (pg/mL)	48	3.8 $\pm$ 3.0	45	4.6 $\pm$ 6.2
hsCRP (mg/L)	48	6.8 $\pm$ 5.9	45	9.2 $\pm$ 10.8
Cystatin-C (ng/mL)	48	36.0 $\pm$ 10.9	45	36.3 $\pm$ 10.7

Note: BMI = Body mass index; DSST = Digit Symbol Substitution Test; FBG = Fasting blood glucose; FEV₁ = Forced expiratory volume in 1 s; FVC = Forced vital capacity; HAI = Healthy Aging Index; hsCRP = High-sensitivity C-reactive protein; hsIL-6 = High-sensitivity interleukin-6; MoCA = Montreal cognitive assessment; SBP = Systolic blood pressure; SD = Standard deviation.

Table 2. Effect of a 6-mo Intentional Weight Loss Intervention on Estimates of the HAI Score, Its Components, and Other Candidate Mortality Biomarkers

Outcome Variable	Weight Stable		Weight Loss		<i>p</i> Value
	6-mo Mean (95% CI)	6-mo Change (95% CI)	6-mo Mean (95% CI)	6-mo Change (95% CI)	
HAI (score, 0–10)	3.06 (2.68, 3.43)	–0.22 (–0.60, 0.15)	2.53 (2.17, 2.89)	–0.75 (–1.11, –0.39)	0.04
SBP (mmHg)	128.99 (124.99, 132.98)	–3.83 (–7.82, 0.17)	125.36 (121.52, 129.20)	–7.46 (–11.30, –3.62)	0.17
FVC (L)	2.83 (2.70, 2.95)	–0.05 (–0.17, 0.08)	2.98 (2.86, 3.11)	0.11 (–0.01, 0.23)	0.06
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)	108.00 (103.95, 112.06)	1.45 (–2.61, 5.50)	102.67 (98.78, 106.56)	–3.89 (–7.78, 0.00)	0.047
MoCA (0–30)	25.82 (25.16, 26.48)	0.13 (–0.53, 0.79)	25.78 (25.14, 26.42)	0.09 (–0.55, 0.73)	0.92
Candidate Mortality Biomarkers					
Gait Speed (m/s)	1.14 (1.11, 1.17)	–0.03 (–0.06, 0.01)	1.17 (1.14, 1.20)	0.00 (–0.03, 0.04)	0.15
Grip Strength (kg)	25.97 (24.92, 27.01)	–0.33 (–1.37, 0.72)	26.88 (25.86, 27.90)	0.58 (–0.44, 1.60)	0.17
DSST (score, 0–93)	60.75 (59.14, 62.37)	3.28 (1.67, 4.90)	59.64 (58.09, 61.19)	2.17 (0.62, 3.72)	0.29
FEV ₁ (L)	2.12 (2.05, 2.19)	0.01 (–0.06, 0.08)	2.15 (2.09, 2.22)	0.05 (–0.02, 0.11)	0.45
Log hsIL-6 (log-pg/mL)	1.26 (1.12, 1.40)	0.13 (–0.01, 0.27)	1.17 (1.03, 1.30)	0.04 (–0.10, 0.17)	0.32
Log hsCRP (log-mg/L)	1.45 (1.20, 1.69)	0.03 (–0.22, 0.28)	1.33 (1.09, 1.57)	–0.09 (–0.33, 0.15)	0.47
Cystatin-C (ng/mL)	36.52 (34.60, 38.43)	0.07 (–1.85, 1.98)	33.92 (32.07, 35.77)	–2.53 (–4.38, –0.68)	0.04

Note: Adjusted for baseline value and sex. CI = Confidence interval; CRP = C-reactive protein; DSST = Digit Symbol Substitution Test; FBG = Fasting blood glucose; FVC = Forced vital capacity; FEV₁ = Forced expiratory volume in 1 s; HAI = Healthy Aging Index; hsIL-6 = High-sensitivity interleukin-6; MoCA = Montreal cognitive assessment; SBP = Systolic blood pressure.

Figure 1. Forest plot of standardized intervention effect estimates of a 6-month intentional weight loss program on the HAI score and its components. Graphical points represent the change standardized to one baseline standard deviation and lines represent the CI of the standardized change. FBG = Fasting blood glucose; FVC = Forced vital capacity; HAI = Healthy Aging Index; MoCA = Montreal cognitive assessment; SBP = Systolic blood pressure.

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

WL participants lost an average of 8.87 (CI: –10.40, –7.34) kg over the 6-month period and weight remained stable in the WS group (–1.30 [–2.90, 0.29] kg; Group $\times$ Time $p < .01$). After adjustment for baseline value and sex, HAI score in the WL group improved by 0.53 points more compared to the WS group over the 6-month intervention period (WL: –0.75 [–1.11, –0.39] points vs WS: –0.22 [–0.60, 0.15] points); $p = .04$ (see Table 2). Sensitivity analyses including only individuals with complete follow-up data ($n = 65$) resulted in similar effect size estimates (data not shown).

Among the HAI component variables, FBG was modestly reduced (WL: –3.89 [–7.78, 0.00] mg/dL vs WS: 1.45 [–2.61, 5.50] mg/dL;

Figure 2. Forest plot of standardized intervention effect estimates of a 6-month intentional weight loss program on candidate mortality biomarkers. Graphical points represent the change standardized to one baseline standard deviation and lines represent the CI of the standardized change. DSST = Digit Symbol Substitution Test; FEV₁ = Forced expiratory volume in 1 second; hsCRP = High-sensitivity C-reactive protein; hsIL-6 = High-sensitivity interleukin-6.

$p = .047$). Though not significant, FVC was marginally increased (WL: 0.11 [–0.01, 0.23] L vs WS: –0.05 [–0.17, 0.08] L; $p = .06$) in the WL group, and SBP decreased twice as much in the WL group (–7.46 [–11.30, –3.62] mmHg) compared to WS group (–3.83 [–7.82, 0.17] mmHg). However, 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 (vs worsening) in the WL group compared to the WS group, except DSST, which improved more in the WS group. The only significant improvement was observed for Cystatin-C (WL: –2.53 [–4.38, –0.68] ng/mL vs WS: 0.07 [–1.85, 1.98] ng/mL; $p = .04$).

For comparison purposes, standardized intervention effects on all HAI score and component variables as well other candidate mortality biomarkers are presented in Figures 1 and 2. Graphical points represent the change per baseline standard deviation and lines represent the 95% CI of the standardized change. After adjustment for baseline value and sex, the largest magnitude of change in standardized intervention effect was for the HAI score (WL: -0.47 [$-0.70, -0.24$] vs WS: -0.14 [$-0.38, 0.10$] ($p = .04$)), followed by FBG (WL: -0.25 [$-0.50, 0.00$] vs WS: 0.09 [$-0.17, 0.35$]; $p = .047$), and Cystatin-C (WL: -0.24 [$-0.41, -0.06$] vs WS: 0.01 [$-0.17, 0.19$]; $p = .04$), although we did not formally compare these changes statistically.

Associations Between Weight Change and Change in the HAI 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 3. With every 1 kg of WL, HAI score decreased by 0.07 (0.03, 0.12) points ($p < .01$), driven by a 0.80 (0.26, 1.34) mmHg reduction in SBP and 0.02 ($-0.04, -0.01$) L increase in FVC (both $p < .01$). Among other candidate mortality biomarkers, change in gait speed, and FEV₁ were negatively correlated with weight change, while Cystatin-C was positively associated with weight change (all $p \leq .01$).

Discussion

As hypothesized, findings from this analysis utilizing data from a 6-month RCT of WL and WS in older adults with obesity demonstrated intentional WL improved HAI score, with the degree of reduction directly associated with the amount of weight lost. Among component variables, the largest magnitude of change was observed for FBG, followed by smaller improvements in FVC and SBP, although we did not formally compare these changes statistically. Of other candidate mortality biomarkers, Cystatin-C, a traditional kidney function marker, 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.

Results presented here confirm and extend prior work. Previous meta-analysis findings suggest intentional WL in adults with obesity reduces mortality risk by 15%–18% (3,4), and our results point to the potential mechanisms behind this mortality advantage. Changes in component variables in the present analysis are supported by previous literature. Reductions in FBG and SBP are both well-established intentional WL outcomes (33–35). Although the intervention related change in FBG we observed is slightly lower than what might be expected (34), weight change was found to be modestly ($r = .21$) correlated with FBG change, with findings likely influenced by the small sample and short duration of the present study. Furthermore, SBP changes in the present analysis are considered clinically relevant, as the WL group decreased SBP by 7.46 mmHg, which is more than double that of the WS group (-3.83 mmHg).

Relationships between WL and pulmonary or kidney function have rarely been studied, although it is known that fat mass is inversely associated with FVC and FEV₁ values (36), and increased muscle mass is associated with less airflow obstruction (37). Limited RCT evidence supports pulmonary function improvements with WL (38), but FVC and FEV₁ modifications are typically less dramatic in individuals with obesity (vs extreme obesity), with changes likely due to decreased restrictive load, decreased ventilation demand, and improved muscle efficiency (39). This previous literature supports and explains the marginal, but not significant increase in FVC in the present analysis. Creatinine stability in the present study may be explained by participant dietary variations at baseline and follow-up, as diet, as well as other factors like muscle mass, influence creatinine levels, making kidney function estimates difficult (40). Conversely, previous findings support the significant Cystatin-C reduction in the present analysis, as adipose tissue is thought to produce Cystatin-C, and kidney function estimates via Cystatin-C are independent of height, sex, age, and muscle mass (41).

The HAI is one of many clusters of biomarkers or physical measures, such as metabolic syndrome or simply counting comorbidities, used to determine risk of death, disease, or disability.

Table 3. Associations Between Weight Change and Change in the HAI Score, Its Components, and Candidate Mortality Biomarkers After a 6-mo Intentional Weight Loss Program

Outcome Variable	R	p Value	β (95% CI)	p Value
HAI (score, 0–10)	0.37	<.01	0.07 (0.03, 0.12)	<.01
SBP (mmHg)	0.33	<.01	0.80 (0.26, 1.34)	<.01
FVC (L)	–0.42	<.01	–0.02 (–0.04, –0.01)	<.01
Creatinine (mg/dL)	–0.03	.76	–0.00 (–0.01, 0.00)	.62
FBG (mg/dL)	0.21	.06	0.40 (–0.08, 0.87)	.10
MoCA (score, 0–30)	–0.03	.77	–0.02 (–0.10, 0.06)	.65
Candidate Mortality Biomarkers				
Gait Speed (m/s)	–0.29	<.01	–0.00 (–0.01, –0.00)	.01
Grip Strength (kg)	–0.11	.32	–0.07 (–0.19, 0.04)	.22
DSST (score, 0–93)	0.04	.73	0.06 (–0.12, 0.24)	.51
FEV ₁ (L)	–0.43	<.01	–0.01 (–0.02, –0.00)	<.01
Log hsIL-6 (log-pg/mL)	0.02	.88	0.00 (–0.01, 0.02)	.68
Log hsCRP (log-mg/L)	0.01	.94	0.00 (–0.03, 0.03)	.83
Cystatin-C (ng/mL)	0.32	<.01	0.32 (0.09, 0.55)	<.01

Note: Adjusted for sex. CI = Confidence interval; DSST = Digit Symbol Substitution Test; FVC = Forced vital capacity; FBG = Fasting blood glucose; FEV₁ = Forced expiratory volume in 1 s; HAI = Healthy Aging Index; hsCRP = High-sensitivity C-reactive protein; hsIL-6 = High-sensitivity interleukin-6; MoCA = Montreal cognitive assessment; SBP = Systolic blood pressure.

Considering FBG and SBP were most responsive to change, the HAI could arguably be reduced to two component variables to increase clinical utility for a mortality risk assessment measure. However, the modified physiologic index from which the HAI was derived, demonstrated superior ability to predict mortality than its individual components (SBP, FVC, DSST, Cystatin-C, and FBG) (8) and the HAI itself furthermore predicts death exceptionally well in combination with age, supporting the use of a composite score. The slight improvements in many of the component variables with WL likely had a synergistic effect on the net 0.53 point improvement with WL and support the use of such a composite score composed of numerous measures of various organ systems.

To our knowledge, this is the first trial of intentional WL to examine its impact on the HAI. Strengths of the study design include a WS control group and excellent measures of protocol compliance. Weaknesses include the modest sample size and relatively short study duration, impeding our ability to fully evaluate changes that are of modest size, measures that have more within person variability, or are slower to respond to WL. Negative findings should be interpreted in this context. For example, a 6-month study would be insensitive to intervention effects related to the slowing of age-related decline, which may play out over years (ie, global cognitive function). We also did not see any effect of the interventions on hsIL-6, which has been shown to be responsive to caloric restriction in a number of other studies (42,43). 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. And lastly, we did not control for macronutrient timing or distribution, which could have influenced our results, independent of WL. A general limitation of the field is the lack of standardization across caloric restriction protocols, making cross study comparisons difficult.

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, its components, and other potential biomarkers to intentional WL in older adults with obesity, contributing to the current literature by suggesting potential mechanisms behind mortality reduction through WL. Future studies could aim to replicate study findings in larger, longer WL RCT's, and test varying mortality indices (ie, replacing creatinine with Cystatin-C and the MoCA with DSST, as this modified index has also been shown to be predictive of mortality (8) and arguably includes variables more responsive to WL). Ultimately, if confirmed, these findings can be used to create more targeted interventions for, or to evaluate interventions aimed at, mortality risk reduction.

Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

J.K. is currently employed by Medifast, Inc. The terms of this arrangement were reviewed by the Wake Forest University Health Sciences department in accordance with its conflict of interest policies.

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