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Obesity Weight Loss Phenotypes in CKD: Findings From the Chronic Renal Insufficiency Cohort Study

Meera N. Harhay[1,2,3], Yuna Kim[2], Brandy-Joe Milliron[4], Lucy F. Robinson[2] and on behalf of the CRIC Study Investigators[5]

[1]Department of Medicine, Drexel University College of Medicine, Philadelphia, Pennsylvania, USA; [2]Department of Epidemiology and Biostatistics, Drexel University Dornsife School of Public Health, Philadelphia, Pennsylvania, USA; [3]Department of Medicine, University of Pennsylvania Transplant Institute, University of Pennsylvania Philadelphia, Pennsylvania, USA; and [4]Department of Nutrition Sciences, Drexel University College of Nursing and Health Professions, Philadelphia, PA

Introduction: Although people with chronic kidney disease (CKD) and obesity have important motivations to lose weight, weight loss is also associated with health risks. We examined whether patterns of change in systolic blood pressure (SBP), serum albumin level, and fat-free mass (FFM) can help to differentiate between healthy and high-risk weight loss in this population.

Methods: Using data from the Chronic Renal Insufficiency Cohort Study (CRIC), we estimated a joint multivariate latent class model with 6 classes to identify distinct trajectories of body mass index (BMI), albumin, and SBP among participants with obesity (BMI $\geq$30 kg/m^2 at baseline), accounting for informative missingness from death. In a secondary analysis, we fit a 6-class model with BMI and FFM.

Results: Among 2831 participants (median baseline BMI 35.6, interquartile range [IQR] 32.4–40.0 kg/m^2), median follow-up was 6.8 (IQR 4.8–12.9) years, median age was 61 (IQR 54–67) years, 53% were male, 50% were non-Hispanic Black, and 82% were trying to control or lose weight at baseline. Latent classes were associated with mortality risk (5-year cumulative incidence of mortality 6.8% and 1.5% in class 6 and 3, respectively). Class 6 had the highest mortality rate and was characterized by early, steep BMI loss, early serum albumin decline, and late SBP increase. In the secondary analysis, a class characterized by steep BMI and FFM loss was associated with the highest death risk.

Conclusions: Among adults with CKD and obesity, BMI loss with concomitant serum albumin or FFM loss was associated with a high risk of death.

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Obesity (i.e., a BMI $\geq$30 kg/m) prevalence is increasing in the general population and in the population of adults with end-stage kidney disease (ESKD).[1] Adults with CKD and obesity might have important motivations to lose weight, such as improving mobility, quality of life, and access to kidney transplantation. However, several recent studies have identified that weight loss may also be a risk factor for death in adults with CKD and obesity.[2,3–5] Therefore, strategies are needed to support patients with CKD and obesity to ensure that weight loss yields more health benefits than untoward health risks.

Among adults with CKD and obesity, evidence shows that weight loss can lead to distinct health trajectories.[2] Numerous studies have observed a paradoxical association of obesity and survival in ESKD.[6,7] Adults with CKD and obesity might have greater resilience to health stressors than their normal weight counterparts vis-à-vis their higher nutritional stores and muscle mass.[6,8–13] Although weight loss can yield positive cardiovascular and endocrine effects among adults with obesity,[14] it can also signal a decline in lean body mass[15] and cause bone mineralization and metabolism changes that increase fracture risk.[16] It may be possible to distinguish healthy versus high-risk weight loss by examining concurrent trajectories of clinical variables for evidence of increased physiologic resilience or vulnerability, respectively. The ability to

Correspondence: Meera N. Harhay, 245 North 15th Street, Mailstop 437, Philadelphia, Pennsylvania, 19102, USA. E-mail: mnh52@drexel.edu

[5]Members of CRIC Study Investigators are listed in the Appendix

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identify healthy and high-risk weight loss phenotypes among adults with CKD and obesity will improve clinical surveillance of weight loss and the design of future weight loss interventions.

The goal of this study was to identify distinct, multidimensional obesity weight loss phenotypes in CKD and ESKD. We hypothesized that patterns of change in BMI, SBP, and serum albumin level would differentiate weight loss among participants in the CRIC study with obesity into discrete health trajectories that are associated with differences in mortality risk. We used a joint longitudinal latent class model to estimate the relationships between the clinical biomarkers of interest while accounting for the non-ignorable missing data mechanism caused by the observed time-to-event outcome of mortality.[17-19] In a secondary analysis, we identified distinct trajectories of BMI and total lean body mass, derived from bioimpedance spectroscopy assessments, that were associated with differences in mortality risk.

METHODS

Study Population

The CRIC study is an ongoing multicenter prospective study of risk factors for CKD progression and cardiovascular disease. The design and methods of the study and inclusion criteria for study participants have been described previously.[20,21] Briefly, the CRIC study recruited 3939 participants aged from 21 to 74 years with an estimated glomerular filtration rate (eGFR) between 20 and 70 ml/min per 1.73 m^2 from 2003 to 2008. All participants provided informed consent. Study participants completed questionnaires at enrollment about basic sociodemographic information and medical history and returned for yearly visits during which time information was periodically updated. The current analyses were restricted to participants with a baseline BMI $\geq$30 kg/m^2 (Supplementary Figure S1). We excluded subjects with missing SBP or serum albumin at baseline ($n = 78$), leaving 2831 subjects for the primary analysis. For a secondary analysis, individuals with missing FFM assessments at baseline were additionally excluded ($n = 106$). Participants contributed time to the current analysis from the enrollment visit, defined as the index date, until they died or until the end of the CRIC follow-up in May 2020. The study protocol was approved by the institutional review boards of all participating centers and is in accordance with the Declaration of Helsinki.

Exposures

The primary exposures of interest were percentage change in BMI, change in SBP, and change in serum albumin. BMI was calculated as weight in kg, ascertained during CRIC study visits, divided by height in meters squared. Blood pressure was assessed at screening, baseline, and yearly follow-up visits using a standardized protocol.[22] Serum albumin, measured using the Brom Cresol Green-based method,[23] was ascertained at baseline and then yearly during the follow-up period. In the secondary analysis, we included percentage change in FFM as an additional exposure variable. FFM was estimated using bioelectrical impedance analysis. Bioelectrical impedance analysis was performed using a Quantum II bioelectrical impedance analyzer (RLJ Systems, Clinton Township, MI) with the participant lying in the supine position. FFM, fat mass, and total body water were calculated using the equations developed by Chumlea *et al*.[24] Participants with pacemakers or with amputations did not undergo bioelectrical impedance analysis testing.

Covariates

We adjusted our models using the following clinical variables as time-invariant covariates ascertained from CRIC enrollment visits: participant age (years), sex, race/ethnicity, BMI (kg/m^2), serum albumin (g/dl), SBP (mm Hg), diabetes status, and eGFR (ml/min per 1.73 m^2) using the CRIC eGFR equation.[25] In addition, we adjusted for initiation of dialysis or kidney transplantation as time-varying covariates.

After deriving the latent classes, we examined for evidence of differences between classes in the following additional baseline clinical variables: waist circumference, fasting glucose, serum triglycerides, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and self-reported cardiovascular disease. Among participants with available data, we also compared dietary intake (total daily calories, % total daily calories from protein), physical activity (intentional exercise, moderate and vigorous exercise), and health-related quality of life between latent classes. Dietary quality was assessed by CRIC investigators using the National Cancer Institute's Diet History Questionnaire. Physical activity was assessed using the Multiethnic Study of Atherosclerosis Typical Week Physical Activity Survey,[26] that asks participants to characterize time spent in various levels of physical activity during a typical week over the past month, and summarizes total minutes per week and total metabolic equivalents of task-hours/week at 3 intensity levels: light (metabolic equivalents of task <3), moderate (metabolic equivalents of task between 3 and <6), or vigorous (metabolic equivalents of task >6). Health-related quality of life was assessed using the Kidney Disease Quality of Life-36 survey (i.e., the 4-item Burden of Kidney Disease [Burden], 12-item Symptoms and Problems of Kidney Disease [Symptoms], and 8-item Effects of Kidney Disease [Effects] scales),[27] with

higher scores indicating better health-related quality of life in each domain.[28]

Outcome

The primary outcome was time to all-cause mortality. Death events of CRIC participants were ascertained from next of kin, death certificates, and state death files.[29]

Statistical Analysis

To achieve our goal of elucidating patterns of change in BMI, SBP, and serum albumin that are associated with differences in mortality risk, we used a multivariate joint latent class model which contains 2 components estimated simultaneously. The first component is a multivariate latent trajectory model which describes how the sample can be partitioned into subgroups with similar patterns of change over time in the 3 clinical variables. The second component estimates the association between the clinical trajectory which a subject most closely resembles and mortality, after adjusting for covariates described in the preceding section, using a proportional hazards regression model. The associations with mortality inform the interpretation of the observed trajectories in terms of predicting high versus low risk of death.

This joint model framework has advantages over a 2-stage modeling approach when combining information from longitudinal biomarker measurements and mortality. Comparisons of nonmortality longitudinal outcomes are susceptible to biases from informative censoring or truncation because of death or other competing risks that occur during the observation period.[30–33] The sharing of information between the 2 models can help mitigate potential biases caused by missing outcome data in the longitudinal model (e.g., BMI) because the event that caused the missing outcome data (death or censoring) is explicitly incorporated in the joint model. This approach to modeling the longitudinal biomarker outcome entails the estimation of an unobserved, or latent, biomarker trajectory that provides an estimate of how the biomarker trajectory may have looked if there was no informative censoring (e.g., death) and all observations were nonmissing.

The use of latent class methods for the clinical trajectories allows us to decompose this population into identifiable phenotypes. We defined weight change trajectories as percentage change in BMI from baseline over time. Along with BMI, we assessed trajectories of hemodynamic and nutritional markers as absolute changes in SBP (mm Hg) and serum albumin (g/dl) over time from baseline. All statistical analyses were performed using R version 3.6.2 and the lcmm R package[17] version 2.0.0 (R Core Team, Vienna, Austria). Technical details of the joint modeling approach are described in the supplementary material (Supplementary Exhibit S1).

Secondary Analyses

In a secondary analysis, we explored associations between BMI change, FFM change, and mortality. First, we fit a joint latent class trajectory model of percentage change in BMI with 6 classes. Then, we fit Cox models using the estimated latent classes as predictors with and without an interaction between the estimated latent classes and percentage change in FFM as a time-varying covariate, adjusting for all other covariates in the primary model. The interaction between the estimated latent classes and percentage change in FFM was tested by comparing the 2 Cox models using analysis of deviance. Next, we estimated a multivariate joint latent class model of relative changes in BMI and FFM with 6 classes. The class membership and latent trajectory submodels were defined in a similar way as the primary analysis. The proportional hazard submodels for death included the following covariates: baseline age, sex, race/ethnicity, baseline diabetes status, baseline eGFR, baseline BMI, baseline FFM, and initiation of dialysis or receipt of kidney transplantation.

Sensitivity Analysis

We examined the association between the estimated latent classes from the primary analysis and risk of death after further adjustment for self-reported intention to lose weight at baseline. A standard Cox model was fitted with the estimated latent classes as predictors adjusting for baseline age, sex, race/ethnicity, baseline diabetes status, baseline eGFR, baseline BMI, baseline SBP, baseline albumin, time of dialysis/transplant, and weight loss or control intention at baseline. Finally, we estimated a multivariate latent class model with percentage weight change (i.e., instead of % BMI change), SBP, and serum albumin level; and examined associations between the new classes and mortality in a standard Cox model as described above.

Missing Data

We excluded follow-up records with missing data on BMI, serum albumin, and SBP in estimating the multivariate longitudinal trajectories submodels. On average, the number of measurements per participant was 6.7 (SD = 3.5), 7.4 (SD = 4.1), and 8 (SD = 4.3) for BMI, albumin, and SBP, respectively. Average number of FFM measurements per participant was 4.7 (SD = 3.4).

RESULTS

Among the 2831 CRIC participants included in the analysis, median age was 61 years (IQR 54–67), 47%

Table 1. Baseline characteristics of the study cohort, overall, and by latent class

Characteristics	Total ($N = 2831$)	Latent trajectory class 1 ($n = 668$)	2 ($n = 331$)	3 ($n = 1046$)	4 ($n = 476$)	5 ($n = 116$)	6 ($n = 194$)
Age	61.0 (54.0,67.0)	62.0 (55.0,68.0)	61.0 (56.0,68.0)	61.0 (54.0,67.0)	59.0 (53.0,64.0)	55.5 (47.0,61.0)	60.0 (53.0,66.0)
Female	1325 (46.8%)	282 (42.2%)	162 (48.9%)	495 (47.3%)	237 (49.8%)	41 (35.3%)	108 (55.7%)
Race Ethnicity							
Hispanic	289 (10.2%)	53 (7.9%)	26 (7.9%)	123 (11.8%)	40 (8.4%)	25 (21.6%)	22 (11.3%)
Non-Hispanic Black	1407 (49.7%)	330 (49.4%)	188 (56.8%)	502 (48.0%)	226 (47.5%)	54 (46.6%)	107 (55.2%)
Non-Hispanic White	1072 (37.9%)	272 (40.7%)	115 (34.7%)	400 (38.2%)	191 (40.1%)	32 (27.6%)	62 (32.0%)
Other	63 (2.2%)	13 (1.9%)	2 (0.6%)	21 (2.0%)	19 (4.0%)	5 (4.3%)	3 (1.5%)
BMI (kg/m^2)	35.6 (32.4,40.0)	35.6 (32.5,40.1)	35.9 (32.4,40.7)	35.5 (32.5,40.1)	35.0 (32.0,38.3)	35.7 (32.8,39.9)	37.2 (33.5,42.1)
Diabetes	1684 (59.5%)	415 (62.1%)	205 (61.9%)	587 (56.1%)	270 (56.7%)	83 (71.6%)	124 (63.9%)
CVD	996 (35.2%)	277 (41.5%)	149 (45.0%)	284 (27.2%)	165 (34.7%)	42 (36.2%)	79 (40.7%)
Systolic BP (mm Hg)	126 (115,141)	123 (111,135)	152 (140,164)	125 (115,137)	119 (108,131)	141 (129,159)	127 (115,141)
Diastolic BP (mm Hg)	70.0 (62.0,79.3)	68.0 (60.0,76.0)	78.7 (68.7,86.7)	70.7 (62.0,78.7)	68.0 (61.3,76.0)	76.7 (68.7,86.0)	70.0 (62.0,78.9)
Trying to lose weight	2334 (82.4%)	545 (81.6%)	273 (82.5%)	851 (81.4%)	402 (84.5%)	96 (82.8%)	167 (86.1%)
eGFR (ml/min per 1.73 m^2)	46.0 (35.6,57.0)	43.5 (33.6,54.9)	44.4 (35.0,54.8)	48.9 (39.0,59.8)	48.2 (38.4,58.5)	36.5 (28.5,49.3)	39.3 (31.1,50.5)
Serum albumin (g/dl)	3.90 (3.70,4.20)	4.10 (3.90,4.40)	3.90 (3.70,4.10)	3.80 (3.60,4.10)	4.10 (3.80,4.30)	3.10 (2.80,3.30)	3.90 (3.60,4.10)
Glucose (mg/dl)	107 (92.0,142)	112 (95.0,147)	107 (90.0,143)	106 (92.0,143)	103 (89.0,131)	113 (89.8,150)	108 (91.0,138)
Missing	6 (0.2%)	2 (0.3%)	0 (0%)	1 (0.1%)	3 (0.6%)	0 (0%)	0 (0%)
HDL (mg/dl)	43.0 (36.0,52.0)	42.0 (35.0,52.0)	44.0 (37.0,52.0)	43.0 (35.0,52.0)	44.0 (37.0,53.0)	41.5 (36.0,49.3)	42.0 (36.0,51.0)
Missing	847 (29.9%)	211 (31.6%)	92 (27.8%)	367 (35.1%)	113 (23.7%)	20 (17.2%)	44 (22.7%)
LDL (mg/dl)	97.0 (77.0,123)	92.0 (73.0,117)	99.0 (79.0,125)	98.0 (79.0,122)	100 (79.0,127)	104 (77.0,142)	95.0 (68.8,122)
Missing	852 (30.1%)	213 (31.9%)	92 (27.8%)	368 (35.2%)	114 (23.9%)	21 (18.1%)	44 (22.7%)
Triglycerides	137 (97.0,195)	141 (99.0,201)	130 (97.0,181)	135 (95.0,198)	134 (98.0,183)	154 (106,209)	137 (95.0,212)
Missing	847 (29.9%)	211 (31.6%)	92 (27.8%)	367 (35.1%)	113 (23.7%)	20 (17.2%)	44 (22.7%)

BMI, body mass index; BP, blood pressure; cm, centimeter; CVD, cardiovascular disease; dl, deciliter; eGFR, estimated glomerular filtration rate; HDL, High Density Lipoprotein; Hg, mercury; KDQOL, Kidney Disease Quality of Life; kg, kilogram; LDL, low density lipoprotein; m, meters; METS, metabolic equivalent of task; mg, milligram; mm, millimeter.

were female, 50% were non-Hispanic Black, and median BMI was 35.6 kg/m^2 (IQR 32.4–40.0) (Table 1). Diabetes was present in 60% of the cohort at baseline, and over 80% reported that they were trying to control or lose weight. With respect to outcomes during the follow-up period (median 6.8 years, IQR 4.8–12.9 years), 26% initiated dialysis, 15% were wait-listed for kidney transplant, and 5% received a transplant. At the end of the follow-up period, 34% of the cohort had died.

Determination of the Number of Latent Classes

We compared models with up to 7 latent classes to determine the number of classes that would yield the most clinically meaningful and distinct trajectories of BMI, serum albumin, and SBP (Supplementary Table S1). The Bayesian information criterion values suggested better fit with increasing number of classes, but after examining the predicted multivariate trajectories and hazard functions, we concluded that there was minimal incremental benefit of including greater than 6 latent classes to determine clinically meaningful patterns. Therefore, our chosen model has 6 classes.

Latent Trajectories of Percentage BMI Change, Serum Albumin Level, and SBP

The predicted longitudinal trajectories of percentage BMI change, serum albumin change, and SBP change for each of the 6 latent classes are shown in Figure 1 (predicted trajectories of each variable individually with 95% confidence bands are shown in Supplementary Figure S2). The first class contained 24% of participants and was characterized by BMI loss up to 20% during the follow-up period, increase in SBP up to 20 mm Hg, and 0.5 mg/dl decline in serum albumin. The second class contained 12% of participants and was characterized by decline in BMI like class 1, decline in SBP, and relatively stable serum albumin. Class 3 comprised 37% of participants and was characterized by a small (<5%) decline in BMI, small increase in SBP, and small increase in albumin level. Class 4 included nearly 17% of participants and was characterized by a 10% BMI gain, increase in SBP, and decline in serum albumin which was more modest than observed in class 1. Class 5 included 4% of participants and had up to 10% BMI loss early and then stable BMI, a similar pattern of decline in SBP decline followed by stability, and steep increase in serum albumin level. Finally, class 6, with nearly 7% of

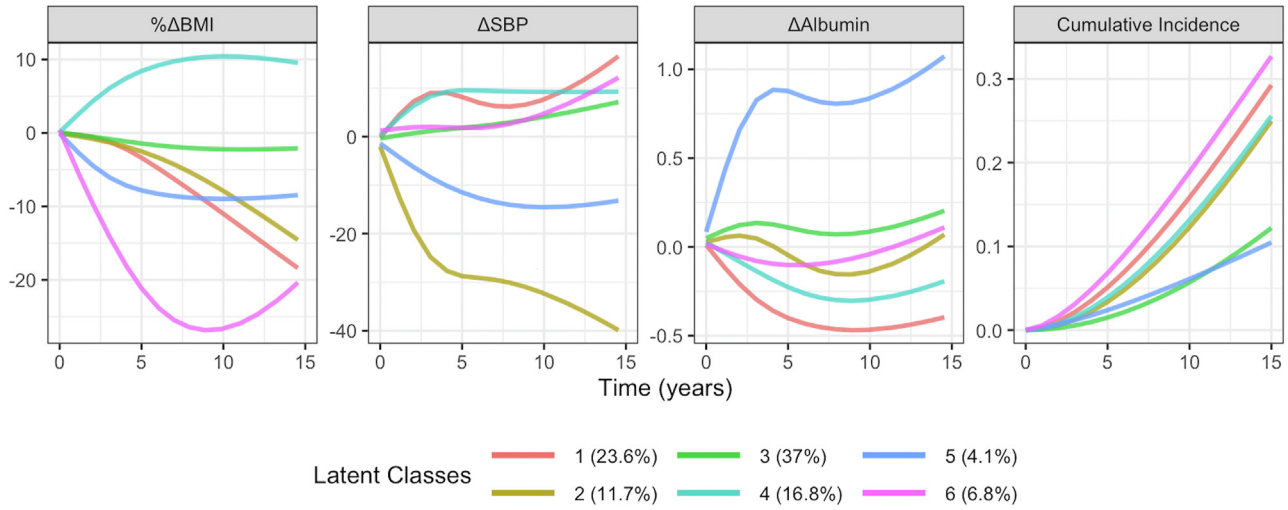

Figure 1. Predicted latent class trajectories and cumulative incidence of death from the 6-class model. Predicted cumulative incidence of death is for a 50-year-old, non-Hispanic White female with diabetes, BMI of 35 kg/m^2, SBP of 130 mm Hg, serum albumin of 4.0 g/dl, and eGFR of 60 ml/min per 1.73 m^2 at baseline and without dialysis initiation or transplant during the follow-up period.

participants, was characterized by steep and early BMI loss of >20%, initially stable then rising SBP, and early decline in serum albumin followed by increasing levels.

Clinical Characteristics by Latent Class Membership

Compared to the most common class (class 3), individuals in class 6 were more likely to be younger (60 vs. 61 years) and female (56% vs. 47%) (Table 1). Individuals in class 6 were also more likely to have a higher BMI (37.2 vs. 35.5 kg/m^2), higher serum albumin (3.9 vs. 3.8 g/dl), higher SBP (127 vs. 125 mm Hg) and a lower eGFR (39.3 vs. 48.9 ml/min per 1.73 m^2) at baseline relative to individuals in class 3. Members of classes 3 and 6 reported similar daily caloric intake and percentage calories from protein and had comparable lipid profiles (Figure 2). Compared to class 3, individuals in class 6 also had lower quality of life from burdens of kidney disease, were more likely to report no intentional exercise, and engaged in less moderate and vigorous exercise.

Associations Between Latent Trajectories and Mortality

The lowest mortality was observed in class 3, which was characterized by stable BMI and had the largest fraction (37%) of subjects. Relative to class 3, mortality was higher in classes 1, 2, 4, and 6, and similar in class 5. The class-specific predicted mortality for a

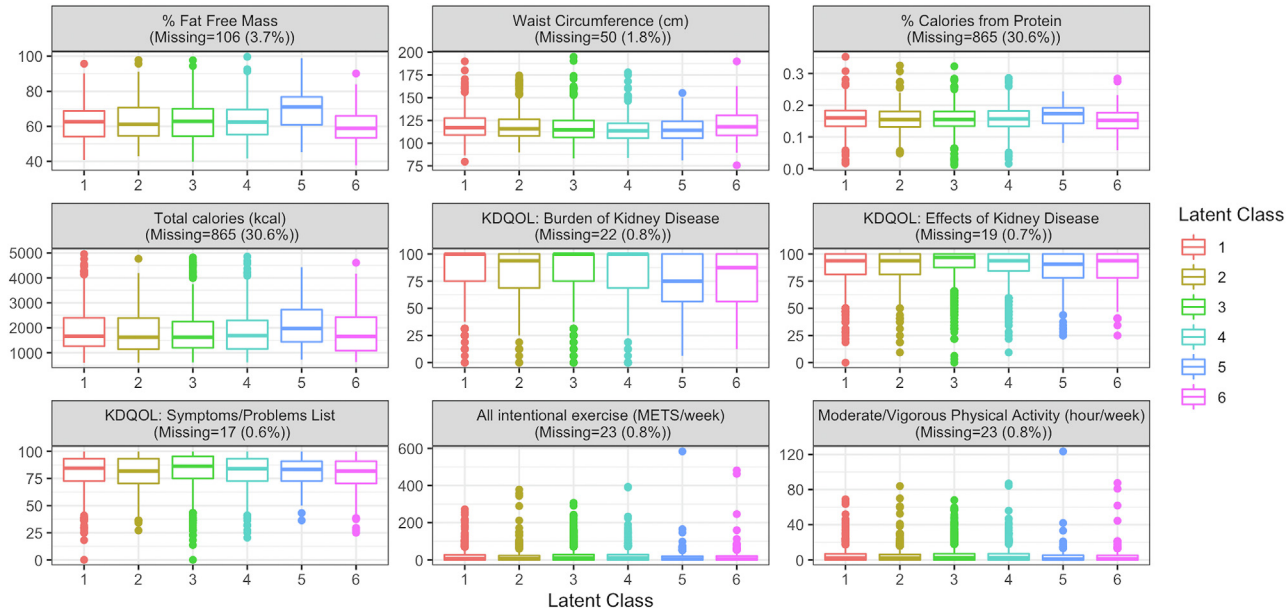

Figure 2. Baseline lean body mass, anthropometry, dietary intake, and physical activity characteristics by latent class membership.

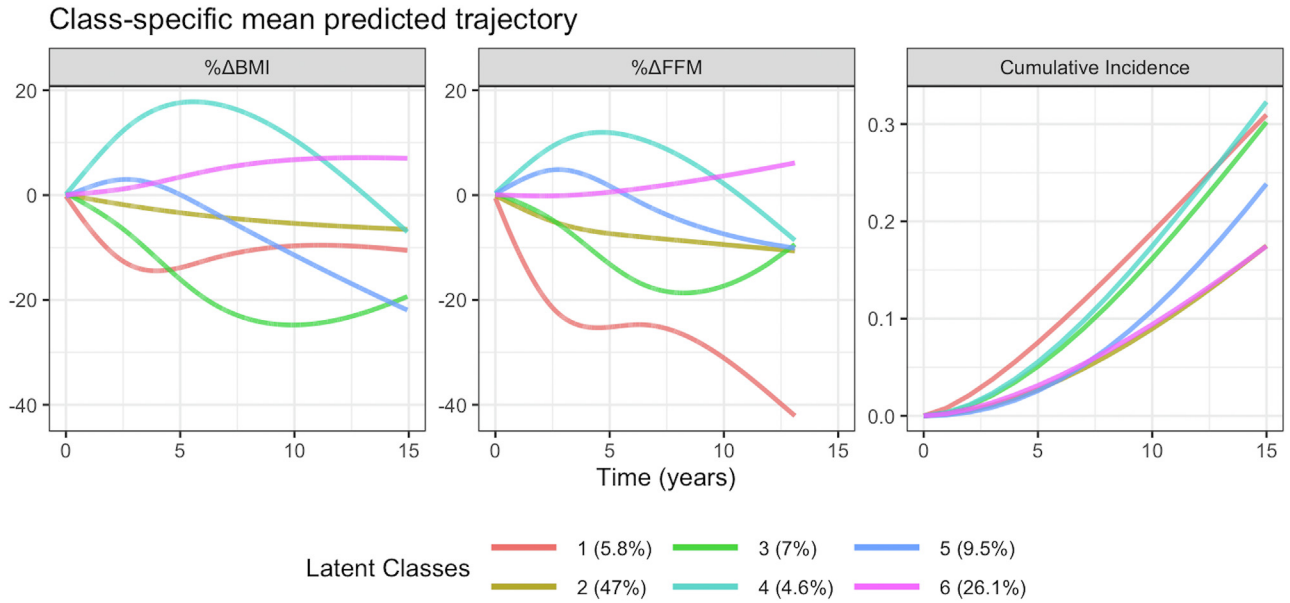

Figure 3. Predicted latent class trajectories and cumulative incidence of death from the 6-class model with BMI and FFM. Predicted cumulative incidence of death is for a hypothetical 50-year-old, non-Hispanic White female with diabetes, BMI of 35 kg/m^2, FFM of 53.1 kg, and eGFR of 60 ml/min per 1.73 m^2 at baseline and without dialysis initiation or transplant during the follow-up period.

hypothetical 50-year-old, non-Hispanic White female with diabetes and a starting BMI of 35.0 kg/m^2, and eGFR of 60 ml/min per 1.73 m^2 are shown in Figure 1 (corresponding estimates for a hypothetical male are shown in Supplementary Figure S3). At 5 years, mortality in class 3 in this example is 1.5%, compared to 2.4% in class 5, and 6.8% in class 6.

Secondary Latent Trajectory Analysis Using Percentage BMI Change and Percentage Fat-Free Mass Change

In the univariate latent class model, change in FFM modified the association between BMI trajectories and death (P-value for interaction = 0.042). In the 6-class model including both BMI and FFM (Figure 3), the most common trajectory was class 2 (47% of individuals) and was characterized by a slow decline in BMI and FFM over time. Class 1 was characterized by early substantial BMI decline followed by BMI gain with a steep FFM decline over time. Class 3 (7% of cohort) was characterized by steep BMI decline and smaller percentage FFM decline than in class 1. Class 4 comprised 4.6% of participants and was characterized by early BMI and FFM increases and subsequent decline. Class 5 had an early small increase in FFM and BMI, followed by steady BMI decline but proportionally less FFM decline compared to classes 1 and 3. Class 6 (26% of cohort) was characterized by BMI and FFM increases. Classes 2, 5, and 6 were associated with the lowest mortality over time, whereas class 1 was associated with the highest mortality.

Sensitivity Analyses

Associations between latent classes and mortality were consistent after further adjustment for participant self-reported intention to control or lose weight (Figure 4). Furthermore, we observed similar latent classes in models that used percentage body weight instead of percentage BMI (Supplementary Figure S4, Panel A). Specifically, we observed that a latent class that was characterized by rapid decline in body weight, late increase in SBP, and early decline in serum albumin level was associated with higher mortality than a class characterized by slower decline in weight, stable SBP, and increase in albumin (adjusted hazard ratio = 1.90; 95% confidence interval 1.45, 2.50) (Supplementary Figure S4, Panel B).

DISCUSSION

In this study of CRIC participants with obesity, we found distinct trajectories of BMI, serum albumin, and SBP that were associated with substantial differences in the risk of mortality. Under the assumed model, each participant was associated with a class described by characteristic patterns of change in BMI, albumin, and SBP. Specifically, we identified that a pattern of rapid weight loss with relatively small changes in SBP and decreases in serum albumin was associated with a nearly 3-fold higher risk of death as compared to a pattern characterized by less rapid weight loss, albumin increase, and decline in SBP. In a secondary analysis examining BMI and FFM trajectories, we found that BMI decline with stable FFM was associated

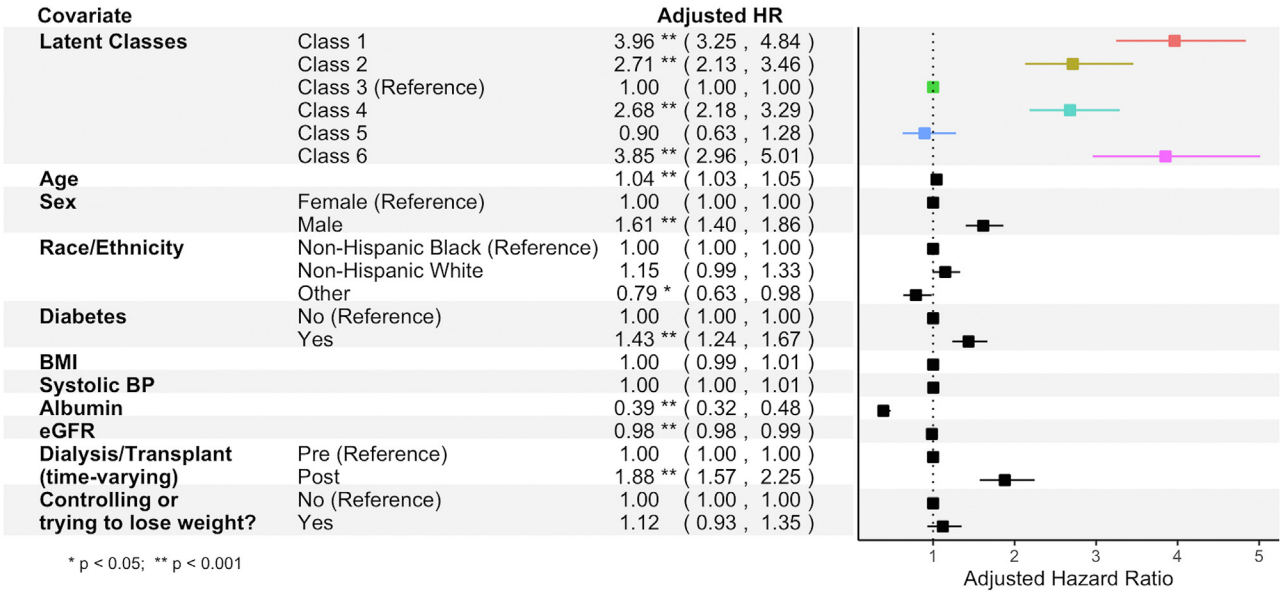

Figure 4. Results of sensitivity analysis including self-reported intentional weight loss. The figure shows hazard ratios with 95% confidence intervals from a Cox model with the estimated latent classes from the 6-class model as predictors, adjusting for covariates, intention to control or lose weight, and dialysis/transplant.

with lower death risk than BMI loss with transient or sustained FFM loss.

The results of our study show that hemodynamic, nutritional, and body composition trajectories can help to distinguish between healthy and high-risk weight loss among adults with obesity and CKD. For example, we found that weight loss that occurs with SBP decline and serum albumin increase is associated with a lower death risk than weight loss occurring with either serum albumin or FFM declines, respectively. Patients with CKD and obesity may be counseled to lose weight to prevent disease progression, cardiovascular disease, and immobility, an independent risk factor for death.[34,35] Obesity is also an important barrier to kidney transplant (KT).[36–39] However, prior studies have identified weight loss as a risk factor for mortality in CKD.[4,5] In addition, substantial weight loss before KT is associated with higher post-KT mortality, irrespective of obesity status.[3] Furthermore, existing nutritional guidelines for patients with kidney disease do not identify which clinical features should alert providers to high-risk weight loss,[40,41] potentially leading to missed opportunities to provide corrective and supportive care to prevent adverse outcomes in the setting of high-risk weight loss. Indeed, in a survey study of renal dietitians from across the US, no respondents rated it to be "very easy" to distinguish between healthy and high-risk weight loss in the ESKD population.[42] Our study suggests that whether weight loss is required or desired by adults with CKD and obesity, they should also be monitored with respect to concurrent changes in hemodynamics, nutrition, and body composition. Future weight loss trials in this population should also assess impacts of interventions on these and other clinical biomarkers and not on weight loss alone.

Our study found consistent evidence that rapid or substantial weight loss is a risk factor for death among adults with CKD and obesity. Specifically, both the latent trajectories that incorporated SBP and serum albumin and those that incorporated FFM showed that adults with >10% decline in BMI early in the observation period were most likely to die during follow-up, whereas the 2 latent classes that had more modest weight loss had the lowest risks of death. These findings are consistent with prior evidence showing a graded relationship between pretransplant weight loss and posttransplant outcomes,[3] as well as a recent study that demonstrated how the shape of BMI change is an important predictor of mortality in dialysis populations. Specifically, among 16,414 dialysis patients from Australia and New Zealand, Brilleman and colleagues utilized a univariate latent class joint modeling approach to describe 5 broad patterns of BMI trajectory after dialysis initiation.[2] In this study, the authors found that obese patients with early and sustained BMI decline had the highest risk of death.[2] In our study of adults with CKD and obesity, even those with modest weight gain (i.e., <10%) had a lower risk of death than those with substantial weight loss, whereas the lowest risks were observed in classes with <10% weight loss and concomitant increase in serum albumin. In combination, this evidence suggests that modest weight loss goals (i.e., up to 10% of starting BMI) might be the

safest option for adults with CKD and obesity, and that patients with substantial or rapid weight loss should be closely assessed for signs of health and nutritional vulnerabilities.

Skeletal muscle loss often occurs with calorie restriction for weight loss,[43] and may lead to sarcopenia, a known predictor of mortality in CKD.[44] Prior research has suggested that nutritional differences and body composition might explain some of the survival advantages observed among ESKD patients with obesity.[45] In our study, we found that the weight loss phenotypes were associated with differences in mortality independent of self-reported intentions to control or lose weight. Our secondary analysis suggests that differences in the retention of lean body mass while losing weight might be a key indicator of healthy versus high-risk weight loss among adults with CKD and obesity. For example, we observed 2 weight loss phenotypes with high (>10%) FFM losses that had the highest risks of death, whereas a phenotype with more modest weight loss and <10% loss of FFM had the lowest risk of death. Muscle losses might be more profound among those with unintentional weight loss, a domain of the physical frailty phenotype, than those with intentional weight loss. For example, in a multicenter study of KT recipients, those with pre-KT unintentional weight loss were more likely to have low grip strength (50% vs. 43%), more likely to report exhaustion and low physical activity at the time of KT, and were more likely to gain weight and die post-KT than those with intentional weight loss.[46] The findings of our study underscore the importance of FFM for assessing risks of weight gain in adults with CKD and obesity; we found that a phenotype characterized by a higher percentage BMI increase than percentage FFM increase (i.e., indicating gain in fat mass) was associated with a high risk of death, whereas weight gain with proportional FFM gain was associated with a low risk of death. Future research is needed to determine which weight loss strategies are associated with optimal preservation of muscle mass and nutrition among adults with CKD and obesity.

Our study has several strengths. To our knowledge, this is the first study to utilize a multivariate latent trajectory modeling strategy to derive healthy and high-risk weight loss phenotypes in adults with co-existing CKD and obesity. Our study design enabled us to adjust for important confounders, including intentionality of weight loss, that are not typically available in registry data. We were also able to leverage the long follow-up time of the CRIC study to establish weight loss phenotypes and confirm health outcomes. However, our study was subject to certain limitations. For example, we were unable to assess weight loss strategies that may have been used by CRIC participants with obesity to lose weight. Furthermore, given that weight and other variables were ascertained yearly for CRIC participants, our study was unable to characterize whether transient interim changes in body weight were associated with differences in outcomes. Finally, our study may not be generalizable to adults with CKD and obesity who were not eligible to participate in the CRIC study (e.g., those with polycystic kidney disease).[21] Nonetheless, our study represents a novel methodology to understand risks associated with weight loss among adults with CKD and obesity and provides targets for clinical surveillance of weight loss in this population. Our findings should be confirmed within the framework of weight loss intervention studies.

In conclusion, in this longitudinal study of adults with CKD and obesity, we showed that the rate and extent of weight loss and concurrent trends of nutritional, hemodynamic, and body composition indicators are important to understand long-term mortality risks. Although many such individuals have important motivations to lose weight, weight loss attempts should be monitored clinically and those with rapid weight loss should be assessed for signs of worsening physiologic vulnerability.

APPENDIX

List of CRIC Study Investigators:

Lawrence J. Appel
Jing Chen
Harold I. Feldman
Alan S. Go
James P. Lash
Robert G. Nelson
Mahboob Rahman
Panduranga S. Rao
Vallabh O. Shah
Raymond R. Townsend
Mark L. Unruh

DISCLOSURE

MNH wishes to disclose a consultancy agreement with Nephria Bio, unrelated to the present work. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Exhibit S1. Technical Details on Statistical Analysis.

Figure S1. Participant inclusion diagram.

Figure S2. Predicted latent class trajectories and cumulative incidence of death from the 6-class model with 95% confidence intervals. Predicted cumulative incidence of death is for a hypothetical 50-year-old, non-Hispanic White female with diabetes, BMI of 35 kg/m^2, SBP of 130 mm Hg, serum albumin of 4.0 g/dl, and eGFR of 60 ml/min per 1.73 m^2 at baseline and without dialysis initiation or transplant during the follow-up period.

Figure S3. Predicted latent class trajectories and cumulative incidence of death from the 6-class model. Predicted cumulative incidence of death is for a hypothetical 50-year-old, non-Hispanic White male with diabetes, BMI of 35 kg/m^2, SBP of 130 mm Hg, serum albumin of 4.0 g/dl, and eGFR of 60 ml/min per 1.73 m^2 at baseline and without dialysis initiation or transplant during the follow-up period.

Figure S4. Sensitivity analysis using body weight instead of BMI to derive latent class models. Panel a shows predicted latent class trajectories. Panel b shows hazard ratios with 95% confidence intervals from a Cox model with the estimated latent classes from the 6-class model as predictors adjusting for the baseline covariates, intention to control or lose weight, and dialysis/transplant.

Table S1. Comparison of joint multivariate latent trajectory models with up to 7 classes. The models with different numbers of latent classes are not nested (i.e., individuals are reassigned into the latent class for which they have the highest posterior class-membership probability).

STROBE Checklist.

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