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Using Growth Mixture Modeling to Identify Classes of Sodium Adherence in Adults With Heart Failure

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Introduction

Adherence to a low-sodium diet is an important self-care behavior for patients with heart failure (HF). Excess sodium intake promotes higher ventricular filling pressures, pulmonary congestion, clinical symptoms of fluid retention, and puts patients with HF at high risk for acute decompensation and hospitalizations.¹ As such, adherence to a low-sodium diet is a key factor in reducing hospitalizations² and one of the most frequently recommended self-care behaviors.³⁻⁶ Both the 2012 European Society of Cardiology and 2009 American College of Cardiology/American Heart Association guidelines recommend less than 2 g/day of dietary sodium.^{7,8} Likewise, the Heart Failure Society of America recommends that all patients with clinical symptoms of HF restrict sodium to 2-3 g/day.⁶ It is estimated, however, that only about 22-55% of HF patients are adherent to a low-sodium diet.⁹⁻¹²

Adherence, as defined by the World Health Organization (WHO), is a multidimensional phenomenon, determined by multiple dimensions related to social and economic conditions, the health care system in addition to condition, therapy or patient-related factors.¹³ Like medication adherence in this patient population, adherence to a low sodium diet is influenced by a number of factors.¹⁴ Although several factors have been associated with non-adherence to a low-sodium diet in the adult population with HF, there are limitations to these research findings. Most prior studies on 24-hour urine sodium excretion are cross-sectional in design and conducted with small samples. Deterministic methods, including mixed effects modeling have previously been used to identify patient-level factors associated with high sodium intake using an *a priori* determined cutoff of adherence.¹⁵ This study builds on that analysis by applying a growth mixture modeling methodology to

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identify the “most likely” trajectory membership and quantify uncertainty in trajectory membership over time.

The specific aim of this study was to use growth mixture modeling to identify distinct patterns of change in 24-hour urine sodium excretion, as a proxy for dietary sodium intake, over six months of observation. The secondary aim was to build on a previous mixed effects analysis¹⁵ and examine patient-level determinants of observed trajectories of urine sodium.

Methods

Design and Study population

The methodology of this study has been previously reported in detail.¹⁴ In brief, this was a prospective, observational study of the association between excessive daytime sleepiness and HF self-care among 279 community-dwelling adults with chronic HF. The participants were enrolled from three outpatient settings in Philadelphia, Pennsylvania and Newark, Delaware between 2007 and 2010. Most of the participants were followed in specialty HF clinics and most were on optimal medical therapy. Given the observational nature of this study, the usual care provided by HF specialty clinics was not augmented. Participants did not receive supplemental HF self-care education outside of what was provided as part of routine care.

Inclusion criteria for the study specified adults with previously or currently symptomatic HF confirmed by echocardiographic and clinical evidence.¹⁴ The participants needed to be able to actively participate in the study, so inclusion criteria specified that patients must be able to read and speak English and have sufficient cognition and health literacy to complete the questionnaires. Otherwise eligible individuals were excluded if they lived in a long-term care setting and were not responsible for their own self-care, including preparing and making choices about food. People were also excluded if they had renal failure requiring dialysis, imminent plans to move out of the area, a history of drug or alcohol abuse within the past year or an imminently terminal illness. People with major depressive illness were also excluded because self-care behaviors are influenced by major depression.¹⁶ This study was in compliance with the Declaration of Helsinki.¹⁷ Institutional Review Board approval was obtained from all three sites and all participants gave written informed consent. Data were collected at baseline, 3-and 6-months by research assistants during home visits. Institutional Review Board approval was obtained for this secondary analysis.

Measurement of dietary sodium

A 24-hour urine sodium collection is considered a reliable and valid estimate of sodium intake^{18,19} and has been used as an objective measure of sodium intake in other studies with patients with HF.^{1,20} Sodium is under tight homeostatic control. If individuals do not perspire heavily, urine sodium accounts for approximately 95% to 98% of daily dietary sodium intake.²¹ Variations in 24-hour urine sodium are primarily attributed to changes in sodium intake over the previous 24 hours.²² Daily urine sodium levels are estimated to fluctuate only about 11%.²³ Validation for 24-hour urine collection has been performed by urine recovery of oral doses of para-amino benzoic acid.^{19,23,24}

The methodology for collecting and measuring dietary sodium intake has been reported elsewhere¹⁵ and is summarized here. Dietary sodium intake was estimated using three 24-hour urine sodium levels measured at enrollment, and at three and six months after enrollment. The procedure for the collection and quantification of the 24-hour urine samples is summarized here. At the time of enrollment, participants and their family members were given training for the specimen collection. Participants were provided with all necessary supplies including: urine containers, collection devices, verbal and written instructions (with

pictures) specifying when they should start and finish collecting the specimen. Prior to each urine collection, patients were given a reminder call and training for the procedure was reinforced by the research assistant. Participants self-reported the start and stop time of the urine collection. If the recorded time was less than 22 hours or greater than 26 hours it was considered inaccurate and excluded from the analysis. Specimens were collected from participant's homes by a courier service shortly after the 24-hour sample was complete.¹⁵

Urine sodium analyses were completed at the central laboratory at the Hospital of the University of Pennsylvania using the ion-selective electrode method (Beckman LX[®] 20 Chemistry Analyzer, Beckman Coulter, Inc., Fullerton, CA) to determine the amount of sodium in the urine specimens. A normal urinary sodium level is 40 to 120 mEq/L/day.¹¹ In order to compare urine excretion with the recommended diet of 2-3 g/day sodium intake,⁶ urine sodium excretion in millimoles was converted to g ($g = \text{mmol} * .02299$) to estimate dietary sodium intake. As a quality assurance measure, urinary creatinine was measured concurrently. Normal urinary creatinine is $1 \pm 10\%$ g²⁵ so any samples with creatinine levels <0.9 g in 24 hours were considered incomplete.²⁶

Statistical Analysis

Standard descriptive (proportions, means and standard deviations), unadjusted odds ratios and *t* tests were used to describe the sample and compare trajectories. Latent growth mixture modeling was used to identify distinct trajectories of urinary sodium using data from three time points.

Latent class growth modeling is used to examine patterns in longitudinal data with repeated measures to identify classes or subgroups within a population. Unique trajectories or pathways differentiate classes from one another. Using repeated measures to identify subgroups within a population has been used across multiple disciplines. Latent class growth mixture analysis also has been used across multiple disciplines to identify trajectories of development;²⁷ nighttime continence;²⁸ physical aggression in young boys;²⁹ the natural history of prostate disease;³⁰ depression recovery profiles³¹ and preventative interventions for reducing classroom violence.³² It has also been used extensively in the substance abuse literature to identify trajectories and predictors of high-risk behavior.³³⁻⁴⁴ Within the heart failure literature, it has been used to identify patterns of cognitive change,⁴⁵ as well as patterns of medication nonadherence.⁴⁶

The purpose of growth mixture modeling is to identify homogenous subgroups within larger heterogeneous populations and represent unobserved heterogeneity among subjects in a sample. Finite mixture random effects are used to represent the departure of individuals' latent growth parameters from the population mean growth parameter.^{32,47} Class membership of an individual cannot be measured directly; however, it can be inferred based on membership in a specific trajectory.⁴⁸ According to Wang and colleagues growth mixture modeling can be described as having three steps. The first step is analogous to random effects modeling which specifies individual-level observed data as a sum of fixed effects, random effects and measurement errors at each observation point.⁴⁸ The second step represents the distribution of class-specific random effects and covariate effects on class-specific mean growth trajectories. The third step includes the covariate effects on class membership using regression models.⁴⁸

Growth mixture modeling has many benefits over alternative methods, as reviewed by Preacher.⁴⁹ Growth mixture modeling can model changes in factors over time as random effects, allow for variations between individuals and subgroups (instead of individuals and the population average as in mixed-effect modeling) and judge comparative fit between iterative models with various statistics; the focus of growth mixture modeling is on

capturing inter-and-intra-individual differences over time.⁵⁰ Conventional deterministic approaches minimize within group and maximize between-group variance. In contrast, growth mixture modeling employs a model-based approach to calculate the probability of membership in each trajectory, identify “most likely” trajectory membership, and quantifies uncertainty in trajectory membership. In this article the terms subgroups and classes are used synonymously to describe people who share a specific growth trajectory.

Growth mixture modeling was performed using MPlus v.6.12 (Los Angeles, CA). Model fit between 2 to 4 trajectories were compared (k vs $k-1$ trajectories) using the Lo-Mendell-Rubin adjusted likelihood ratio test ($p<0.05$), parametric bootstrapped likelihood ratio test ($p<0.05$), Bayesian Information Criteria (BIC), convergence (entropy closest to 1.0), the proportion of the sample in each trajectory (not less than 5%), and average posterior probabilities (closest 1.0).^{50,51} Predictors of observed trajectories of dietary sodium were quantified using logistic regression modeling in MPlus. Unadjusted and multivariate odds ratios (OR) and 95% confidence intervals (CI) were calculated for each model factor, taking into account our method of multiple imputation, described below.

The following ten determinants of non-adherence were tested based on the five dimensions of adherence posed by the WHO.⁵² Four of the five WHO adherence dimensions were included in this analysis. The fifth factor was not included because data on the health care system was not available for this secondary data analysis. Patient related factors included gender, age and BMI. Social and economic factors included race, income and highest level of education. Condition related factors included New York Heart Association (NYHA) functional class, HF type (diastolic or systolic), etiology of HF and diabetes as a comorbidity. Therapy related included diuretic use.

Robust Handling of Missing Data

In an effort to reduce bias, a principled method of multiple imputation⁵³ was performed to account for missing urine sodium excretion values (23% of the sample had at least one missing value). Data were imputed using the method of chained equations (Stata v. 11.2).⁵⁴⁻⁵⁶ The method of chained equations is a contemporary technique that imputes missing data based on multiple covariates in the dataset (i.e. a full information method of imputation). The latent class variable was fit on imputed data in Mplus v.6.12. Multiple sensitivity analyses were performed to examine potential differences in the significance and effect size of predictors of urine sodium trajectories comparing complete case with imputed data samples. There were no differences in the predictors identified in the models except for the size of the confidence intervals; thus, for economy of presentation, only the final analysis using imputed data is shown here.

Results

The overall demographic and clinical characteristics of the sample population overall at baseline are presented in Table 1. This sample of adults ($n=279$) with HF was predominantly male (64%), had a mean age of 62, non-ischemic HF etiology and was functionally compromised (59% NYHA class III). The unadjusted odds ratios for the analysis are presented in Table 2. The covariates that had a statistically significant unadjusted association with the non-adherent trajectory were diabetes ($p=0.008$), income ($p=0.031$) and BMI ($p<0.001$).

Modeling of three and four trajectories resulted in poor model fit and small trajectories (*data not shown*). Entropy for the two-class model was 0.752 and there were high average posterior probabilities of membership in both trajectories (94% and 91%), indicating very limited uncertainty in trajectory membership. Based on the observed characteristics, we

labeled the first and largest trajectory “adherent” (n=178, 66%) and second trajectory “non-adherent” (n=91, 34%).

As displayed in the Figure there was heterogeneity within each trajectory, as demonstrated by the error bars, which indicate two standard deviations around each mean urine sodium level at each point in time. Paired t-tests demonstrate statistically significant differences between the two trajectories at each time point ($p<0.001$). Those in the adherent group started off at baseline with a mean sodium consumption of 2.42 g/day (standard deviation (SD) ± 0.19 , 95% CI: 2.39-2.45) versus 4.41 g/day (SD: ± 0.34 , 95% CI: 4.33-4.48) in the non-adherent trajectory ($t=61.68$, $p<0.001$). At three months, the mean difference between the two trajectories was 2.16 g/day (SE: 0.36, $t=59.99$, $p<0.001$) and by six months was 1.98 g/day (SE: ± 0.03 , $t=62.56$, $p<0.001$). Within the adherent and non-adherent trajectories there were no differences from baseline to 6 months (SE: ± 0.02 , $t=-1.39$, $p=0.166$ and SE: ± 0.05 , $t=-0.47$, $p=0.640$), indicating that there were limited changes in dietary sodium intake over time.

Based on the WHO model, predictors of membership in the non-adherence trajectory were identified. The conceptual model was also supported using data driven statistical approaches including univariate associations. Compared with normal weight patients (BMI <25), being overweight and obese was associated with a 4-fold incremental increase in the likelihood of being in the non-adherent trajectory (OR: 4.63, 95% CI: 1.66-12.91, $p<0.002$). Being less than 65 years of age (OR: 4.66, 95% CI: 1.04-20.81, $p=0.044$) or having diabetes (OR: 4.15, 95% CI: 1.29-13.40, $p=0.016$) were both associated with over four times the odds of being in the non-adherent urine sodium trajectory compared with people who are over 65 or do not have diabetes, respectively. There were no significant differences in the odds of being in the non-adherent trajectory based on gender, cognition, diuretic use, income level, education, race, HF etiology, HF type or NYHA functional status.

Discussion

The primary aim of this study was to identify trajectories of sodium adherence in a sample of community dwelling HF patients and two groups were identified. Based on the more liberal Heart Failure Society of America sodium recommendations of 3g/day sodium intake,⁶ one trajectory was labeled “adherent” and the other “non-adherent” to a low sodium diet. Both groups were consistently adherent or non-adherent over six months of follow-up. That is, there was no change in the level of adherence or non-adherence over time.

To the best of our knowledge, this is the first study that describes adherence to a low-sodium diet using a growth mixture approach; however, this method has been applied to medication adherence in this study sample.⁴⁶ The predictors of the non-adherence to a low sodium diet were being overweight or obese, age less than 65 years and having diabetes. These results that obesity and diabetes predict higher sodium consumption are consistent with an analysis that employed a mixed-effect analytic approach;¹⁵ however, in this study we also identified younger age as a risk factor for being non-adherent to a sodium restricted diet.

HF patients who were overweight or obese, age less than 65 years or have diabetes were identified as being more likely to have trouble following a restricted sodium diet and may need more focused, tailored self-care interventions.⁵⁷ One approach to tailoring self-care interventions that we are testing in a pilot randomized control study is a tailored motivational interviewing and skill-building approach to improving self-care behaviors including adherence to a low-sodium diet.

The finding that being obese is strongly associated with greater odds of being non-adherent to a restricted sodium diet implies that these patients may be consuming more food and by default more sodium, or that they are specifically consuming more foods that are higher in sodium. This finding is consistent with the Intersalt international study of electrolyte excretion and blood pressure, in which investigators reported a positive correlation between BMI and sodium excretion.¹⁹ They proposed that overweight individuals consuming higher sodium intake most likely explains this finding.⁵⁸ In contrast, Chung et al²⁰ found no differences in BMI between people who self-reported being adherent or non-adherent to low-sodium guidelines. The approach in our study is different than that used by Chung and colleagues in that we did not apply a 2,000 mg cutoff for sodium adherence. Instead, we identified distinct and naturally occurring trajectories of urinary sodium excretion that happened to track with current dietary sodium recommendations. Moreover, the current study was longitudinal in design. Thus, methodological differences may explain our incongruent findings.

Other authors studying sodium adherence in the HF population have not reported our finding of an association between younger age and non-adherence to a low sodium diet. In studies of adherence to self-maintenance behaviors, an association between age and adherence to medication has been reported. Several studies report that younger patients are more adherent to taking medication^{59,60} while others found no consistent difference in medication adherence by age.⁶¹⁻⁶³ In this specific sample, we found no difference in overall medication adherence by age.⁶⁴ The association with younger age and the non-adherent trajectory could be that younger patients with HF may also be more newly diagnosed and not yet adept in the skills of identifying and avoiding hidden sodium in foods. Patients with HF who are over 65 years may be living that long because they have been more stringent with the self-maintenance behavior of eating a low salt diet.

The finding that diabetes is a strong predictor of the non-adherence to a low sodium diet is most likely explained by overconsumption of sodium, rather than a physiologic mechanism. In fact, in the diabetic state of hyperinsulinemia, sodium reabsorption is enhanced in the nephron segments of the kidney.⁶⁵⁻⁶⁸ Clinically, patients with both HF and diabetes may struggle to closely monitor both their sugar and their sodium intake. There may receive conflicting messages from multiple providers about nutritional priorities. The implications of this finding may be that interventions are needed to specifically address the dietary complexities of managing both HF and diabetes in this patient population.

Several factors that we anticipated would predict sodium adherence did not reach statistical significance, including higher income and education. We expected that people who reported having inadequate income would potentially be more likely to be non-adherent to a low sodium diet because low-sodium food is more expensive and time consuming to prepare than processed, higher-sodium foods; however, there were no differences between people who reported more income than needed, enough to meet needs or less than needed. Several investigators have suggested that people with more years of education would be more adherent with medication;^{62,69} however, education has not been found to be associated with sodium adherence. In this study, we found no differences in sodium adherence based on education. The lack of association between years of education and adherence to low-sodium diet is consistent with the propositions of the WHO adherence model,¹³ which suggests that higher education in and of itself does not necessarily lead to higher health literacy or behavior change. In this specific study, poor health literacy was an exclusion criterion. As an observational study, there was also no intervention tested, limiting our ability to comment on behavior change.

There are probably many other barriers to following a low-sodium diet that are more important than knowledge. For instance, an identified barrier for patients is the perception that foods will taste bland and unappealing without added salt.⁵⁷ This barrier has been addressed by clinicians who promote flavoring with salt substitutes, using low-sodium cook books and allowing taste buds to adapt to lower-sodium foods.⁷⁰ Other contextual barriers identified in a qualitative descriptive study of older women with hypertension and HF include eating alone with no motivation to cook healthy meals. These women also identified that healthcare providers need to provide more education on a low-sodium diet, as well as large-print informational materials.⁷¹ A study by De Brito-Ashurt (2011) identified barriers to dietary sodium restriction in people of Bangladeshi origin with chronic renal disease living the UK.⁷² Though the disease and patient population are different from this study population, the barriers, including deeply rooted dietary beliefs, attitudes and culturally established taste for salt,⁷²⁻⁷⁴ are likely to be universal across patient populations.

Other authors found low-sodium diet adherence rates to be about 28% or 29%.^{11,12} The findings from this study offer a different perspective from that of population-average adherence. What we can say is that 66% of the sample fit the adherent profile to sodium recommendations and 34% fit the non-adherent profile. These numbers cannot be compared with other population averages or direct calculations of sodium adherence. This non-deterministic approach offers advantages to understanding how non-adherence can be examined and provides a list of useful predictors that are relevant to clinicians for tailoring self-care interventions and education.

Strengths and Limitations

The primary strength of this study is the use of growth mixture modeling, which enables moving away from quantifying the overall population average to examining and quantifying heterogeneity and identifying distinct subgroups. Another strength of this research is that it includes longitudinal data collected at three time points, on a relatively large group of community dwelling stable patients with HF. Many other studies that have examined sodium adherence included only one, 24-hour urine collection in small sample sizes. With an even larger sample size, we may have been able to identify more latent categories of adherence and more predictors of trajectory membership. Further research is needed to determine if the two classes identified in this study will hold across multiple populations of patients with HF. In other words, are these predictors consistent and generalizable to different populations of patients with HF, or localized findings? The primary limitation of this dataset was that originally 23% of the total sample had missing outcome data; however, this was accounted for, at least in part, by contemporary and robust imputation techniques.

Conclusion

Two distinct trajectories of sodium intake were identified. The non-adherent trajectory identifies a distinct pattern of dietary sodium intake that is not consistent with current sodium guidelines. Identified predictors (overweight or obese, less than 65, or having diabetes) can be used by clinicians to target interventions to patients who are most likely to struggle with eating a lower sodium diet. Results can also be used to tailor interventions and patient education programs to the highest risk groups. They can also be incorporated into HF management programs. Future studies identifying the specific barriers within these patient populations are also warranted so that the specific barriers can be targeted with interventions.

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Figure.

Trajectories of adherence to low sodium diet recommendations for patients with heart failure

Table 1

Characteristics of the overall sample at baseline (n=279)

	Overall n (%)		Overall n (%)
Age		Diuretic	
< 65 years	165 (59)	Yes	225 (81)
>=65 years	114 (41)	No	54 (19)
Gender		Cognitive Impairment* (n=271)	
Male	179 (64)	Yes	107 (40)
Female	100 (36)	No	164 (61)
Race		Heart failure type	
Black/Other	104 (38)	Diastolic/Mixed	86 (31)
White	175 (63)	Systolic	193 (69)
Income		Body mass index* (n=278)	
More than needed	98 (35)	Normal	74 (26)
Enough to meet needs	137 (49)	Overweight	73 (26)
Less than needed	44 (16)	Obese	131 (47)
NYHA functional class		Highest level of education	
Class I+II	65 (23)	Less than high school	27 (10)
Class III	164 (59)	High school graduate	102 (37)
Class IV	50 (18)	More than high school	150 (54)
Heart failure etiology		Diabetes	
Ischemic HF	102 (37)	Yes	171 (61)
Non-ischemic HF	177 (63)	No	108 (39)
Hypertension		COPD	
Yes	180 (65)	Yes	58 (21)
No	99 (35)	No	221 (79)

NYHA = New York Heart Association, COPD = Chronic obstructive pulmonary disease

* Variables containing missing data

Table 2

Unadjusted odds of membership in the non-adherent urine sodium trajectory (n=279)

	Unadjusted Odds Ratio	95% CI	p-value
Gender			
Female		(reference)	
Male	1.51	0.57-4.03	>0.2
Body Mass Index			
Normal		(reference)	
Overweight	5.27	2.23-13.06	<0.001
Age			
>=65 years		(reference)	
< 65 years	4.80	0.45-51.80	0.20
Diabetes			
No		(reference)	
Yes	3.71	1.41-9.80	0.008
Race			
White		(reference)	
Black/Other	2.60	0.97-7.00	0.059
Income	2.07	1.07-4.02	0.031
NYHA Functional Class	1.27	0.69-2.37	>0.20
Heart failure etiology	1.57	0.37-6.68	>0.20
Heart failure type	2.68	0.89-8.03	0.078
Diuretic	3.58	0.35-36.62	>0.20
Cognitive Impairment * n=271	1.00	0.44-2.27	>0.20
LVEF * n=278	0.99	0.97- 1.00	0.089

CI = confidence intervals, NYHA = New York Heart Association, LVEF = Left Ventricular Ejection Fraction

* Variables containing missing data

Table 3

Identifying predictors of non-adherence to the low-sodium dietary recommendation using multivariate logistic regression modeling (n=270)

	Odds Ratio	95% CI	p-value
Gender			
Female		(reference)	
Male	3.52	0.93-13.26	0.063
Body Mass Index			
Normal		(reference)	
Overweight	4.63	1.66-12.91	0.002**
Age			
>=65 years		(reference)	
< 65 years	4.66	1.04-20.81	0.044**
Diabetes			
No		(reference)	
Yes	4.15	1.29-13.40	0.016**
Race			
White		(reference)	
Black/Other	1.20	0.28-5.15	>0.20
Income	0.95	0.33-2.75	>0.20
NYHA Functional Class	0.71	0.43-1.17	>0.20
Heart failure etiology	1.51	0.39-5.86	>0.20
Heart failure type	1.27	0.28-5.80	>0.20
Diuretic	1.18	0.15-9.02	>0.20
Cognitive Impairment	0.65	0.21-2.04	>0.20
LVEF	0.99	0.96-1.03	>0.20

CI = confidence intervals, NYHA = New York Heart Association, LVEF = Left Ventricular Ejection Fraction

** Statistically significant p<0.05