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Hospital-Based Higher Calorie Refeeding and Mealtime Distress in Adolescents and Young Adults with Anorexia Nervosa or Atypical Anorexia Nervosa

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Abstract

Objective: The StRONG study demonstrated that higher calorie refeeding (HCR) restored medical stability faster in patients hospitalized with anorexia nervosa (AN) and atypical AN (AAN), with no increased safety events compared to standard-of-care lower calorie refeeding (LCR). However, some clinicians have expressed concern about potential unintended consequences of HCR (e.g., greater mealtime distress). The purpose of this study was to examine patient treatment preference and compare mealtime distress, food refusal, and affective states between treatments.

Method: Participants (N = 111) in this multisite randomized clinical trial were ages 12–24y, with AN or AAN, admitted to hospital with medical instability who received assigned study treatment (HCR or LCR). Treatment preference was assessed prior to randomization in the full sample. In a subset of participants (n = 45), linear mixed effect models were used to analyze momentary ratings of mealtime distress (pre, during, and post-meals) and daily affective state during the hospitalization.

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Clinical Trial registration: This trial is registered at ClinicalTrials.gov NCT02488109.

Results: About half (55%) of participants reported a preference for LCR. Treatment assignment was not associated with food refusal, mealtime distress, or affective states in the subsample. Food refusal increased significantly over the course of refeeding ($p = .018$). Individuals with greater depression experienced more negative affect ($p = .033$), with worsening negative affect over time for individuals with higher eating disorder psychopathology ($p = .023$).

Discussion: Despite understandable concerns about potential unintended consequences of HCR, we found no evidence that treatment acceptability for HCR differed from LCR for adolescents and young adults with AN and AAN.

Article Summary:

This study examines treatment preference, food refusal, and predictors of mealtime distress in adolescents with anorexia nervosa randomized to higher or lower calorie inpatient refeeding. (25/25 words)

Keywords

anorexia nervosa; atypical anorexia nervosa; medical stabilization; refeeding; high calorie refeeding; treatment acceptability; mealtime distress; food refusal; positive affect; negative affect

There is growing consensus that lower calorie refeeding (LCR) for anorexia nervosa (AN) is unnecessarily conservative and may prolong hospitalization,[1] although it is still the standard of care in many hospital settings. Current recommendations for LCR start around 1200 kcal per day and advance by 200 kcal every other day.[2] Higher calorie refeeding, starting between 1500–2000 kcal per day, advances more quickly—by 200 kcals per day.[3] Building on numerous studies demonstrating the feasibility of HCR,[4–6] recent evidence from the Study of Refeeding to Optimize iNpatient Gains (StRONG)—the first randomized clinical trial (RCT) comparing HCR to LCR—demonstrated that HCR is more efficacious than LCR for adolescents and young adults hospitalized with AN and atypical AN (AAN), with significantly briefer hospitalizations (by an average of four days)[7] and without increased safety events or hospital readmissions.[8] However, questions remain around the psychological impact of these refeeding treatments and their treatment acceptability. This is particularly relevant because some clinicians have questioned whether patients perceive HCR as an acceptable treatment, or even whether it could be psychologically detrimental given clinically significant patient distress about eating and gaining weight.[9]

Scientific discovery alone does not change practice,[10] and concerns about treatment appropriateness and acceptability for patients could be barriers to HCR adoption and implementation by providers. Preliminary data from the StRONG RCT suggest that patients can tolerate HCR, with no significant differences in meal completion between participants assigned to HCR versus LCR.[7] Further, a recent pilot study found that adolescent and young adult patients receiving HCR did not report changes in state anxiety over the course of their hospitalization.[11] Adults with AN also report relatively good acceptability and satisfaction with programs using HCR.[12] However, more data on treatment acceptability in the adolescent and young adult population are necessary given that patients in high distress may require more intensive staff support, which may impact providers' decision to

adopt HCR in their hospital setting. In addition, very little is known about psychological response to short-term medical treatment, including mealtime distress patterns, despite the fact that exposure (i.e., eating) is a core component of treatment[13] and that reductions in mealtime distress may predict outcome in adolescents with AN and AAN.[14] This study also sought to learn more about factors that predict mealtime distress and affective states during hospitalization, including the impact of treatment (HCR vs. LCR).

This study builds on prior research and examines patient treatment preference, food refusal, mealtime distress, and affective states in hospitalized adolescents and young adults with AN or AAN randomized to HCR or LCR. We evaluated food refusal and mealtime distress by treatment condition, hypothesizing that participants would indicate a preference for LCR and that participants assigned to HCR would have greater food refusal and mealtime distress. Finally, we explored predictors of affective states over the course of refeeding in hospital. To our knowledge, this is the first study to provide data on hospital refeeding treatment preferences for patients with AN/AAN, and the first to compare longitudinal trajectories of mealtime distress and affective states across treatments.

Methods

Methods for the StRONG RCT have been previously described in detail along with short-term[7,15] and long-term outcomes[8] (ClinicalTrials.gov identifier NCT02488109). Eligible participants ages 12–24 years hospitalized for malnutrition secondary to AN or AAN at one of two inpatient medical eating disorder (ED) units in northern California between February 2016 and March 2019 were approached for enrollment ($N = 301$). Potential participants were excluded if they had an ED-related medical hospitalization within 6 months prior to admission. Adolescent and young adult participants ($N = 120$) were randomly assigned to LCR (1400 kcal/day, increased by 200 kcal every other day) or HCR (2000 kcal/day, increased by 200 kcal every day). Meals and snacks were provided on a bedside tray and observed by a patient care attendant (“sitter”). Liquid formula was given orally to replace any calories refused on the meal tray at meals or snacks. No participants required tube feeding due to 100% compliance with liquid formula replacement. Regardless of treatment assignment, each participant advanced to their individualized caloric goal prior to hospital discharge. Participating adolescents and young adults provided written informed assent or consent, with written parental informed consent for minors.[4,5] Consent/assent discussions included informing potential participants that length of stay was expected to be longer for those assigned to LCR than HCR. The primary outcome paper reported on the main outcomes of the study—time to restore medical stability and medical outcomes on the efficacy and safety of the refeeding treatments.[7] The current study focuses on distinct outcomes, including treatment acceptability and psychological outcomes during the hospitalization. Patient treatment preferences were examined in all participants who received the assigned study treatment ($N = 111$). The planned psychological aims examining daily food refusal, mealtime distress, and affective states during the hospitalization included participants at only one of the two sites ($n = 45$) due to the infeasibility of collecting momentary data in a group milieu setting at the other site, with human subjects approval from the Institutional Review Board at UCSF. The main study protocol was approved by the Institutional Review Boards at UCSF and Stanford.

Outcome Measures

Treatment preference.—Treatment preference at admission [i.e., *Which treatment (high calorie or low calorie) would you prefer to receive?*], and perceived treatment assignment at discharge [i.e., *Which treatment (high calorie or low calorie) do you think you received?*] were both assessed because participants might have been able to infer assigned treatment based on their meal plan despite being "blinded" to treatment assignment.

Food refusal.—Food refusal was defined as total daily kcal not consumed on the initial tray provided that were subsequently consumed via liquid formula replacement with 100% compliance.

Mealtime distress.—Participants rated their current distress using a Subjective Units of Distress Scale (SUDS) from 0 (totally relaxed) to 100 (worst distress and anxiety imaginable). Participants were prompted by text message to rate SUDS every day 30 minutes prior to, during, and 30 minutes following dinner in the hospital. Text prompts were automatic, based on participants' individualized meal/snack schedules, and sent to their personal cell phone.

Positive and negative affect.—The Positive and Negative Affect Scale for Children (PANAS-C) is a 10-item scale assessing momentary positive and negative affective states. Subscale scores range from 5 to 25 (higher scores indicate greater intensity), with good reliability[16] and validity in child and adolescent samples.[17] Participants completed the PANAS-C daily in the evening.

Independent Variables

All independent variables were assessed at baseline, including demographic and clinical characteristics such as highest historical body weight (with height and age at time of highest weight), duration of illness (defined as time from the reported start of weight loss to hospital admission), percent of median BMI (%mBMI) (calculated by dividing baseline BMI by the median BMI for age and sex, multiplied by 100)[18], and weight suppression,[18] which was calculated as %mBMI loss (i.e., $highest\ \%mBMI - admission\ \%mBMI$). Since the refeeding protocols were standardized by treatment group rather than individually tailored to participants' body weight, a daily refeeding dose variable was calculated as daily kcal prescribed per kg of body weight each day.

ED psychopathology.—The Eating Disorder Examination–Questionnaire (EDE-Q)[19] is the leading questionnaire for assessing ED psychopathology[20] with good reliability and validity in adolescents.[21] Higher global scores at admission indicated more severe psychopathology (range: [0,6]).

Depression.—The Patient Health Questionnaire for Adolescents (PHQ-A)[22] is a 9-item measure of depressive symptoms administered at admission, with good reliability and validity.[23]

Anxiety.—The General Anxiety Disorder 7-item Scale (GAD-7)[24] is a brief anxiety scale administered at admission that has good reliability and validity in adults[24] and adolescents.[25]

Distress tolerance.—The Distress Tolerance Scale (DTS)[26] is a 15-item measure designed to assess strategies used to regulate positive and negative affect, with good reliability and validity.[26,27] Lower scores indicate a tendency to experience negative emotions as intolerable.

Analysis

Descriptive statistics, t-tests, and chi-square tests were used to examine patient treatment preference at baseline by subgroups (age, gender, depression, anxiety etc.). All subsequent analyses for food refusal, mealtime distress, and affect were conducted in a subsample of 45 patients at one site where mealtime distress data were collected. Baseline characteristics (age, gender, race/ethnicity, socioeconomic score, and clinical variables) of the subsample were summarized with mean, standard deviation, frequency, and percentage and compared to the full sample. The subsample patients were randomized to HCR or LCR within the site. Due to natural attrition over time with discharges (day 1: $n = 45$, day 7: $n = 33$, day 14: $n = 7$, day 21: $n = 1$), the subsample patients' food refusal, mealtime distress, and affect for the first 14 days of the refeeding intervention were included in the analyses with linear mixed-effect models (LMM). Outcome variable data were available for 40 participants. Given the small sample size, a set of initial models with one independent variable (IV) of interest at a time were examined. Each initial LMM included time, one IV, and time × IV interaction, accounting for within-subject correlation over time. IVs included treatment, age, weight gain, daily refeeding dose, daily mealtime distress (for the model with food refusal as the dependent variable), weight suppression, ED psychopathology, depression, anxiety, and distress tolerance. A nonsignificant time × IV interaction was excluded from the initial model to evaluate the IV main effect, unless the IV was a time-varying variable. All significant IVs that had significant main effects and/or interactions from the initial models were entered into a final multivariable model to evaluate their adjusted effects on distress outcomes. Using a within-subject correlation of .30, this study was sufficiently powered (.80) to detect medium-sized effects.

Results

Participants were predominantly girls/women (91%, $n = 101$) with AN (54%, $n = 60$) who were 16.4 years on average (SD = 2.5) and had a 15.6-month ($SD = 17.1$) duration of illness. Race and ethnicity included adolescents and young adults who identified as White (n = 70, 63%), Latinx (n = 24, 22%), Asian (n = 13, 12%), and mixed race (n = 4, 4%). Average length of inpatient stay across the full sample was 10.8 days ($SD = 5.2$). For the subsample ($n = 45$), participants were predominantly girls/women (93%, $n = 42$) with AN (44%, $n = 19$) who were 16.4 years on average (SD = 2.5) and had a 17.4-month ($SD = 15.8$) duration of illness. The subsample did not differ from the larger study population by sex, age, diagnosis, or duration of illness (ps > .05).

What treatment do patients prefer to receive?

For participants with pre-randomization treatment preference data (n = 94; 85% participant questionnaire completion rate at pre-treatment), about half reported an LCR preference (55%, n = 52), 15% (n = 14) reported an HCR preference, and 30% (n = 28) reported no treatment preference. LCR was preferred by participants with significantly greater ED psychopathology (LCR: M = 3.93, SD = 1.60; HCR: M = 2.48, SD = 1.94; t = −2.871, p = .006) and lower levels of distress tolerance (LCR: M = 44.50, SD = 13.46; M = 54.21, SD = 12.24; t = −2.455, p = .017). Females were more likely to prefer LCR (81%); males preferred HCR (67%; X^2 = 3.885, p = .049). There were no differences by age, diagnosis, duration of illness, %mBMI, weight suppression, depression, or anxiety.

For participants with discharge questionnaire data (n = 72; 65% participant questionnaire completion rate at discharge), most (78%, n = 56) believed they knew the treatment to which they had been assigned, with no difference by treatment (p = .45). However, accuracy of perceived assigned treatment differed significantly by treatment (X^2 = 8.720, p = .003), with LCR participants being more likely to *incorrectly* perceive assignment to HCR (59%, n = 16; LCR: 41%, n = 11), and HCR participants being more likely to correctly perceive their treatment assignment (79%, n = 23; LCR: 21%, n = 6).

Do patients in HCR have greater food refusal or experience higher mealtime distress than those in LCR?

Food refusal.—Adjusting for time, treatment assignment had no significant effect on total kcal of food refused (p > .10). Adjusting for time and total kcal served, there were no significant effects for age, duration of illness, anxiety, distress tolerance, or daily weight gain on food refusal. There was a significant initial main effect for depression (p = .016), as well as significant interactions between time and ED psychopathology (p = .026), daily mealtime distress (p = .024), daily refeeding dose (p = .010), weight suppression as %mBMI loss (p = .006), and baseline %mBMI (p = .016). Significant effects from the initial models were entered into a final model (see Table 1). After adjusting for time (p = .06) and total daily kcal served (p = .74), greater baseline depression was significantly associated with greater food refusal, with each one-point increase in PHQ-A score associated with 30 additional kcals refused (p = .042). There was also a significant interaction between time and %mBMI, such that food refusal increased over the hospitalization for those with higher baseline %mBMIs (≥85%) but lessened over the hospitalization for those with lower baseline %mBMIs (<85%) (p = .046). No other effects were significant in the final model.

Mealtime distress.—On average across hospital days, mealtime stress peaked *during* meal consumption (M = 46.60, SD = 24.94), with lower distress at post-meal (M = 41.36, SD = 26.19) than pre-meal (M = 44.69, SD = 24.05), with no differences by treatment assignment in mealtime distress patterns either within meals (pre, during, post) or across meals (see Figure 1) (p > .10). Subsequent analyses averaged SUDS scores (intercept = 46.83 at day 1) within meals (pre, during, post) due to the relatively small sample size. Adjusting for time, there were no significant effects for age, duration of illness, depression, %mBMI, weight suppression, ED psychopathology, or daily weight gain (ps ≥ .09). Significant main effects from the initial models with time (anxiety: p = .005, daily refeeding

dose: $p = .027$, distress tolerance: $p = .001$) were entered into a final model. Adjusting for time ($p = .17$), higher refeeding dose was associated with significantly greater mealtime distress across the hospitalization period, with each additional 10 kcal/kg associated with a 2.76-point increase in SUDS ($p = .048$). Refeeding dose across the hospitalization period was 48 kcal/kg on average ($SD = 13$) [range: 22, 96]. There were no significant main effects of distress tolerance ($p = .08$) or anxiety ($p = .13$).

Do affect trajectories across hospitalization differ by treatment?

Negative affect.—Treatment assignment was not associated with negative affect trajectories over the course of the hospitalization ($p > .10$). Adjusting for time, there were no significant initial effects for age, duration of illness, depression, %mBMI, weight suppression, daily refeeding dose, or daily weight gain (ps > .10) on negative affect (intercept = 10.86). Significant effects from the initial models with time (anxiety: $p = .005$, depression × time interaction: $p = .044$, distress tolerance: $p = .009$, ED psychopathology × time interaction: $p = .013$) were entered into a final model but removed one at a time for parsimony due to multicollinearity between depression and anxiety. Adjusting for time ($p = .28$), individuals with greater baseline depression reported significantly greater negative affect overall ($p = .033$), such that each one-point increase in the PHQ-A score was associated with a 0.3 increase in negative affect on the PANAS-C. There was also a significant ED psychopathology by time interaction ($p = .023$), such that those with relatively lower EDE-Q scores (≤ 4.194) had relatively stable levels of negative affect while those with higher EDE-Q scores (i.e., scores above the median, or > 4.194) reported increasing negative affect over the hospitalization (see Figure 2).

Positive affect.—Treatment assignment was not associated with positive affect trajectories over the course of the hospitalization ($p > .10$). Adjusting for time, there were no significant initial effects for age, distress tolerance, depression, %mBMI, weight suppression, daily refeeding dose, or daily weight gain (ps > .06) on positive affect (intercept = 8.92). Significant effects from the initial models (ED psychopathology × time interaction: $p < .001$, duration of illness × time interaction: $p = .014$; anxiety × time interaction: $p = .027$) were entered into a final model. In the final multivariable model, two of the three interactions remained significant (ED psychopathology by time: $p < .001$; duration of illness by time: $p = .002$), such that participants with relatively lower ED psychopathology and a shorter duration of illness (≤ 1 year) reported improvements in positive affect, while those with higher ED psychopathology and a longer duration of illness (> 1 year) reported decreasing levels of positive affect over two weeks of refeeding in the hospital (see Figure 3). Neither the main effect of anxiety nor its interaction with time were significant (ps > .37). Positive affect remained relatively stable over time for participants who either had higher ED psychopathology but a shorter duration of illness, or relatively lower ED psychopathology but a longer duration of illness.

Discussion

Our findings indicate that HCR is acceptable for adolescents and young adults with AN and AAN. Food refusal, mealtime distress, and affective states remained relatively stable

over two weeks of hospitalization in all the patients. This finding extends our previous finding that meal completion did not differ by treatment (HCR vs LCR)[7] by demonstrating that food refusal, mealtime distress, and affective states did not differ across treatment conditions. Patients experienced moderate distress regardless of treatment, and neither level of distress nor refeeding dose interfered with their capacity to complete meals served in hospital. Instead, characteristics that influenced food refusal preceded the administration of the treatment (i.e., greater depressive symptoms and relatively higher %mBMIs).

Refeeding dose (i.e., kcal per kg of body weight)—rather than kcal alone—was a statistically significant predictor of greater mealtime distress, such that patients receiving more kcal relative to their own body weight experienced greater distress. Increased distress was likely therapeutic, with anxiety treatments in adolescents typically developing exposure situations that induce SUDS just below or at the middle of the scale,[28] which was comparable to the mean SUDS reported in this study. However, this effect was not clinically significant—each additional 10 kcal/kg was associated with a <3 point increase in SUDS on a scale from 1 to 100.

Across treatments, refeeding improved positive affect in patients with less severe ED psychopathology and a shorter duration of illness. However, refeeding did not improve positive affect among those with *either* a longer duration of illness (with less severe ED psychopathology) *or* more severe ED psychopathology (with a shorter duration of illness). The extent to which short-term hospital-based improvements in positive affect (or lack thereof) may impact future outcomes (e.g., engagement in psychological treatment, eating disorder recovery) has not yet been explored in adolescent samples. However, it may be of interest as a future direction given prior research identifying depressive affect as a moderator of hospitalization rates in adolescents[29] and treatment outcomes in adults.[30,31]

Notably, negative affect increased for individuals with more severe ED psychopathology, with decreasing levels of positive affect for those with more severe ED psychopathology and a longer duration of illness. These findings suggest that such patients may benefit from more intensive psychological support, even during hospitalization. Notwithstanding, none of these clinical factors—not even mealtime distress, daily weight gain, or treatment assignment—predicted greater total food refusal. Even though LCR was more strongly preferred by those with more severe ED psychopathology at baseline, these individuals did not report higher mealtime distress regardless of treatment assignment, suggesting that the perception or anticipation of increased calories is more distressing than the actual presentation of increased calories on the meal tray. Indeed, most participants assigned to LCR mistakenly believed they had received HCR, consistent with AN/AAN psychopathology and perceiving any adequate caloric plan as “high” calorie.

Strengths of this study include comprehensive assessment of psychological factors, time-varying data, use of mixed effect models, and randomized clinical trial design. However, there are several limitations, including modest sample size with few males; missing data on treatment preference and perceived treatment for 15% and 35% of the sample, respectively; absence of the caregiver perspective; and the absence of data on treatment satisfaction, which may have been negatively impacted by longer hospitalization stays for those receiving

LCR. Finally, the examination of food refusal, meal-time distress, and affect was limited to participants at a single site and restricted to a hospital setting for the duration of a brief stay, without understanding how the two refeeding approaches may have impacted outcomes following discharge from the hospital.

This study found no evidence that HCR was associated with greater mealtime distress or food refusal, which supports the acceptability of HCR for adolescents and young adults hospitalized with AN and AAN. Providers whose sites adhere to lower calorie inpatient refeeding protocols may feel hesitant about whether patients can handle significantly more nutrition, and whether provider burden (e.g., nursing support, physician time spent rounding, placing liquid replacement orders) might also increase. These data should be reassuring that HCR is acceptable to and manageable for patients, over and above efficacy data on HCR being superior to LCR in clinical outcomes.[7] Hybrid effectiveness-implementation approaches are needed in the future to assist with translating existing research knowledge into real-world practice.

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Data availability statement:

Study investigators agree to abide by the principles for sharing research resources as described by the NIH in “Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Programs.”

Abbreviations:

LCR	lower calorie refeeding
HCR	higher calorie refeeding
AN	anorexia nervosa
AAN	atypical anorexia nervosa
ED	eating disorder
mBMI	median body mass index
TGW	treatment goal weight

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Public Significance statement:

The efficacy and safety of higher calorie refeeding in hospitalized patients with anorexia nervosa has been demonstrated. However, it is not known whether higher calorie refeeding (HCR) increases meal-time distress. This study demonstrated that HCR was not associated with increased mealtime distress, food refusal, or affective states, as compared to lower calorie refeeding. These data support HCR treatment acceptability for adolescents/young adults with anorexia nervosa and atypical anorexia nervosa. (69/70 words)

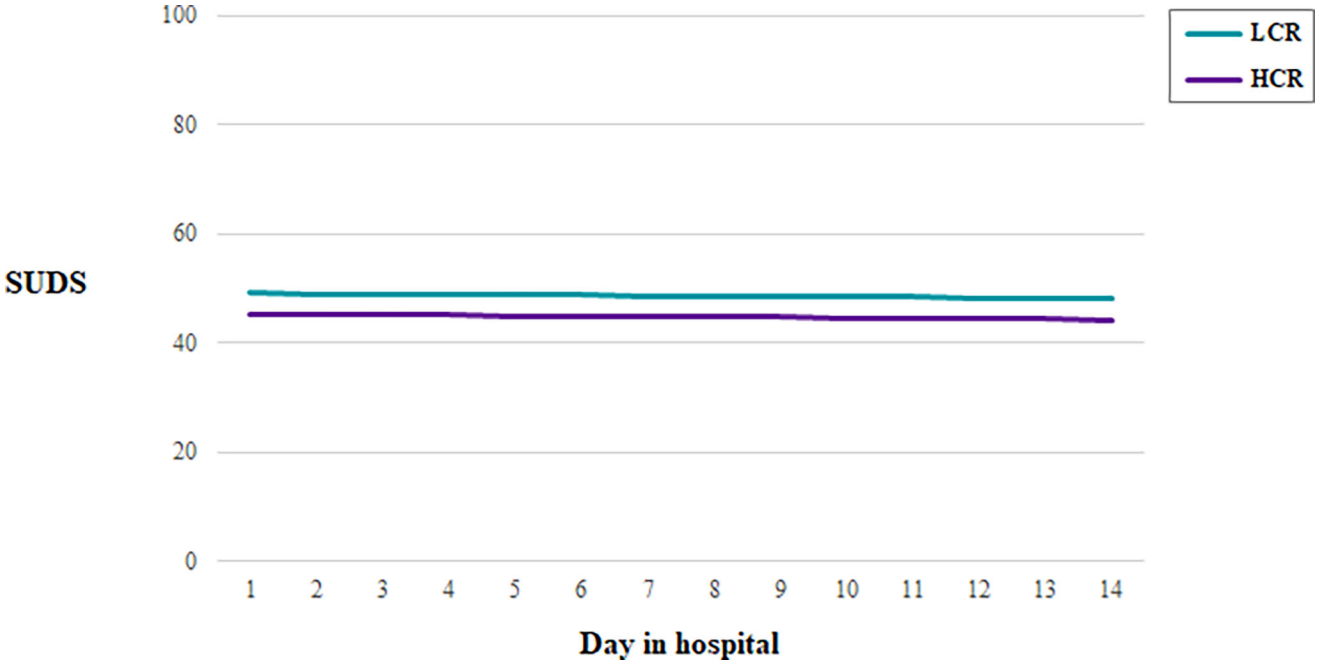

Figure 1.
Change in mealtime distress by treatment (n = 40).

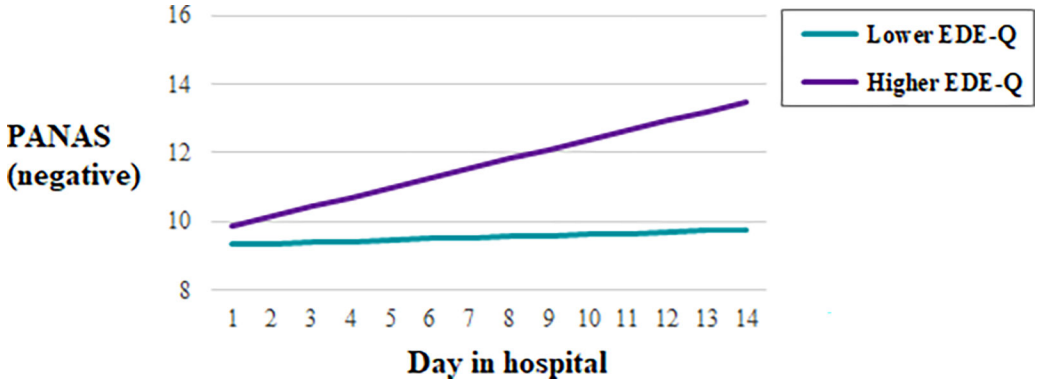

Figure 2.
Change in self-reported negative affect by level of eating disorder psychopathology (n = 40).

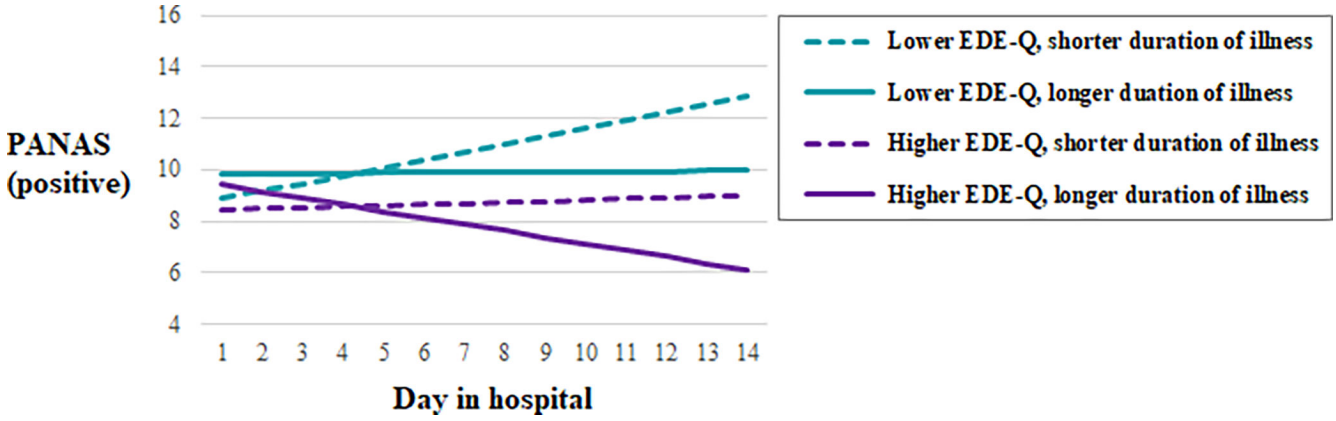

Figure 3.

Change in self-reported positive affect by level of eating disorder psychopathology and duration of illness ($n = 40$).

Table 1.

Final models with participants at one site (n = 40) examining food refusal, mealtime distress, negative affect, and positive affect as dependent variables.

Food Refusal				
	B	*SE*	*F*	*p*
Intercept	−484.300	805.140	-----	.55
Time (day)	−157.760	82.068	3.70	.06
Total daily kcal	0.119	0.355	0.11	.74
Total daily kcal × time	−0.033	0.029	1.30	.26
Refeeding dose	4.385	17.082	0.07	.80
Refeeding dose × time	1.297	1.517	0.73	.40
Baseline %mBMI	410.640	880.840	0.22	.64
Baseline %mBMI × time	160.790	80.060	4.03	.046
%mBMI loss	−9.688	5.371	3.25	.07
%mBMI loss × time	0.965	0.507	3.63	.06
ED psychopathology	−24.066	65.093	0.14	.71
ED psychopathology × time	5.434	5.457	0.99	.32
Mealtime distress	0.510	2.630	0.04	.85
Mealtime distress × time	−0.264	0.413	0.41	.52
Depression	30.236	14.749	4.20	.042
Mealtime Distress				
	B	*SE*	*F*	*p*
Intercept	53.587	23.227	-----	.027
Time (day)	−0.607	0.438	1.92	.17
Total daily kcal	0.276	0.139	3.98	.048
Anxiety	1.059	0.689	2.36	.13
Distress tolerance	−9.855	5.523	3.18	.08
Negative Affect				
	B	*SE*	*F*	*p*
Intercept	11.054	5.003	-----	.035
Time (day)	−0.162	0.148	1.19	.28
ED psychopathology	−0.407	0.470	0.75	.39
ED psychopathology × time	0.092	0.040	5.29	.023
Mealtime distress	−1.063	1.161	0.84	.36
Depression	0.264	0.123	4.62	.033
Positive Affect				
	B	*SE*	*F*	*p*
Intercept	7.426	1.860	-----	<.001

Time (day)	0.724	0.165	19.15	<.001
ED psychopathology	0.409	0.413	0.98	.32
ED psychopathology × time	−0.171	0.046	13.84	<.001
Duration of illness	0.057	0.038	2.23	.14
Duration of illness × time	−0.014	0.004	10.16	.002
Anxiety	−0.079	0.134	0.35	.56
Anxiety × time	0.015	0.017	0.82	.37