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Authors

Garber, Andrea
Cheng, Jing
Accurso, Erin
et al.

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Short-term outcomes of the study of refeeding to optimize inpatient gains for patients with atypical anorexia nervosa

Andrea K. Garber, PhD, RD[1], **Jing Cheng, PhD**[2], **Erin C. Accurso, PhD**[3], **Sara M. Buckelew, MD, MPH**[1], **Amanda E. Downey, MD**[1,3], **Daniel Le Grange, PhD, FAED**[3,4], **Sasha Gorrell, PhD**[3], **Cynthia J. Kapphahn, MD, MPH**[5], **Anna Kreiter, PsyD**[5], **Anna-Barbara Moscicki, MD**[5], **Neville H. Golden, MD**[6]

[1]Department of Pediatrics, Division of Adolescent and Young Adult Medicine, University of California, San Francisco, California, USA

[2]Department of Preventive and Restorative Dental Sciences, University of California, San Francisco, California, USA

[3]Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, California, USA

[4]Department of Psychiatry and Behavioral Neuroscience, The University of Chicago (Emeritus), Chicago, Illinois, USA

[5]Department of Pediatrics, Division of Adolescent and Young Adult Medicine, University of California, Los Angeles, California, USA

[6]Department of Pediatrics, Division of Adolescent Medicine, Stanford University, Stanford, California, USA

Abstract

Objective: The StRONG trial demonstrated the safety and efficacy of higher calorie refeeding (HCR) in hospitalized adolescents and young adults with malnutrition secondary to restrictive

Correspondence: Andrea K. Garber, Department of Pediatrics, Division of Adolescent and Young Adult Medicine, 3333 California Street, Suite 245, Box 0503, San Francisco, CA 94143-0503, USA. andrea.garber@ucsf.edu.

AUTHOR CONTRIBUTIONS

Andrea Garber: Conceptualization; data curation; formal analysis; methodology; writing – review and editing. **Jing Cheng:** Conceptualization; data curation; formal analysis; methodology; writing – review and editing. **Erin Cecilia Accurso:** Conceptualization; investigation; methodology; writing – review and editing. **Sara M. Buckelew:** Conceptualization; supervision. **Amanda E. Downey:** Investigation; project administration; supervision; writing – review and editing. **Daniel Le Grange:** Conceptualization; methodology; writing – review and editing. **Sasha Gorrell:** Conceptualization; formal analysis; project administration; writing – review and editing. **Cynthia J. Kapphahn:** Conceptualization; methodology; writing – review and editing. **Anna Kreiter:** Project administration; writing – review and editing. **Anna-Barbara Moscicki:** Conceptualization; methodology; writing – review and editing. **Neville Hylton Golden:** Conceptualization; data curation; investigation; methodology; project administration; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

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eating disorders. Here we compare refeeding outcomes in patients with atypical anorexia nervosa (atypical AN) versus anorexia nervosa (AN) and examine the impact of caloric dose.

Method: Patients were enrolled upon admission and randomized to meal-based HCR, beginning 2000 kcal/day and advancing 200 kcal/day, or lower calorie refeeding (LCR), beginning 1400 kcal/day and advancing 200 kcal every other day. Atypical AN was defined as %median BMI (mBMI) > 85. Independent t-tests compared groups; multivariable linear and logistic regressions examined caloric dose (kcal/kg body weight).

Results: Among $n = 111$, mean ± SD age was 16.5 ± 2.5 yrs; 43% had atypical AN. Compared to AN, atypical AN had slower heart rate restoration (8.7 ± 4.0 days vs. 6.5 ± 3.9 days, $p = .008$, Cohen's $d = -.56$), less weight gain (3.1 ± 5.9%mBMI vs. 5.4 ± 2.9%mBMI, $p < .001$, Cohen's $d = .51$) and greater hypomagnesemia (29% vs. 11%, $p = .03$, OR = 3.29). These suboptimal outcomes were predicted by insufficient caloric dose (32.4 ± 6.9 kcal/kg in atypical AN vs. 43.4 ± 9.8 kcal/kg in AN, $p < .001$, Cohen's $d = 1.27$). For every 10 kcal/kg increase, heart rate was restored 1.7 days (1.0, 2.5) faster ($p < .001$), weight gain was 1.6%mBMI (.8, 2.4) greater ($p < .001$), and hypomagnesemia odds were 70% (12, 128) lower ($p = .02$).

Discussion: Although HCR is more efficacious than LCR for refeeding in AN, it contributes to underfeeding in atypical AN by providing an insufficient caloric dose relative to the greater body weight in this diagnostic group.

Keywords

anorexia nervosa; atypical anorexia nervosa; caloric dose; higher calorie refeeding; lower calorie refeeding; malnutrition; medical instability; nutritional rehabilitation; refeeding

1 | INTRODUCTION

Anorexia nervosa (AN) is a psychiatric disorder of adolescence and young adulthood with profound medical sequelae and a difficult course of recovery. Caloric restriction and other behaviors can quickly result in medical instability (e.g., abnormal vital signs) requiring hospitalization for short-term nutritional rehabilitation, or "refeeding" (Ornstein et al., 2003; Shamim et al., 2003). For decades, the standard of care was lower calorie refeeding (LCR) beginning at around 800–1200 calories (kcal) per day and advancing cautiously by 200 kcal every other day (American Dietetic Association, 2006; American Psychiatric Association, 2000, 2006). This recommendation was developed for low weight patients with AN and intended to minimize risk for the potentially deadly refeeding syndrome (Beumont & Large, 1991; Fisher et al., 2000; Hall et al., 1994; Kohn et al., 1998; MARSIPAN Working Group, 2014). However, LCR contributed to poor weight gain and protracted hospital stay (Garber et al., 2012). These poor outcomes are now recognized as the "underfeeding syndrome" (MARSIPAN Working Group, 2010), and, together with frequent readmissions, low rates of clinical remission (Murray et al., 2019) and high mortality (Arcelus et al., 2011; Cardous-Ubbink et al., 2004), place eating disorders among the costliest pediatric diagnoses (Bardach et al., 2014).

As a result, clinical practice has been slowly shifting toward higher calorie refeeding (HCR), roughly defined as starting at ≥1400 kcal per day (kcal/day). Research on HCR is relatively

new; the majority of available studies have been published since 2010 (Garber et al., 2016). The study of refeeding to optimize inpatient gains (StRONG) was the largest RCT of refeeding to compare HCR, starting at 2000 kcal/day and advancing 200 kcal/day, versus LCR, starting at 1400 kcal/day and advancing 200 kcal every other day, in adolescents and young adults hospitalized with malnutrition secondary to restrictive eating disorders (R01HD082166; ClinicalTrials.gov NCT02488109). HCR restored medical stability 3 days earlier, with no increase in electrolyte abnormalities, and saved nearly USD 20,000 in healthcare charges per participant as compared to LCR (Garber et al., 2021). Follow-up over 1 year showed no difference in clinical remission or hospital readmission, thus maintaining the initial benefits of HCR (Golden et al., 2021).

While the StRONG trial demonstrated the safety and efficacy of HCR, that refeeding protocol was also designed for patients with AN. The range of body weights among patients with AN has traditionally been low and narrow (Garber et al., 2013; Golden et al., 2013), because diagnosis historically required weight < 85% of expected (American Psychiatric Association, 2000). Since energy requirements are largely dictated by body size (National Academies of Sciences, Engineering, and Medicine, 2023), a single caloric threshold (e.g., HCR) was sufficient to cover the energy needs of most patients with AN and optimize refeeding outcomes (Garber et al., 2019). However, in 2013, atypical AN emerged as a new diagnosis to describe patients with AN psychopathology and significant weight loss but not underweight (American Psychiatric Association, 2013). This patient population grew rapidly to comprise 1/3 of patients admitted to inpatient eating disorder programs (Sawyer et al., 2016; Whitelaw et al., 2014, 2018). Among StRONG participants, 43% were diagnosed with atypical AN, defined as >85% of median body mass index (mBMI) upon admission. We reported that their illness severity, indicated by vital sign instabilities (e.g., bradycardia), laboratory values, and weight history (total amount, rate or duration of weight loss), did not differ from those with AN upon admission (Garber et al., 2019). However, the variance in admission body weight in those with atypical AN was double that of AN (Garber et al., 2019; Sawyer et al., 2016). Given this diversity of body size, it is unlikely that a single refeeding protocol could meet the energy requirements of most patients with atypical AN.

Only one prior study, to our knowledge, has examined outcomes of HCR in patients with atypical AN and AN. Whitelaw et al. (2018) reported that admission weight was not predictive of electrolyte abnormalities, bradycardia, or hypothermia during the course of HCR beginning with a minimum of 1900 kcal. Since the only feature differentiating atypical AN and AN was presentation weight, these findings could suggest that diagnosis does not predict response to refeeding. However, the study was retrospective and included variable refeeding protocols, therefore it is quite possible that patients with atypical AN received higher calorie prescriptions than those with AN. Indeed, this was true for many prior retrospective and observational studies of refeeding in AN (including our own) (Garber et al., 2012, 2013; Golden et al., 2013). This treatment bias is understandable: extensive evidence identifying low weight as a predictor of medical complications during refeeding in AN supported the belief that higher weight patients warranted less caution (and could therefore tolerate higher calories) (Society for Adolescent & Medicine, 2014). This bias could mitigate the true impact of body weight on refeeding outcomes (including medical complications). Therefore, the purpose of the current study was to compare short-term

refeeding outcomes by diagnosis (atypical AN and AN) among hospitalized patients with malnutrition *assigned* to either HCR or LCR in the context of an RCT. Secondarily, we sought to examine the impact of body weight on refeeding outcomes using a clinical construct, refeeding "dose", calculated by dividing the calorie assignment (2000 for HCR or 1400 for LCR) by the individual patient's admission body weight. We hypothesized that short-term refeeding outcomes on either protocol (HCR or LCR) would be worse in atypical AN as compared to AN, and that suboptimal outcomes in atypical AN would be explained by insufficient caloric dose.

2 | METHOD

2.1 | Study design

This is a secondary analysis of data collected for the StRONG trial (ClinicalTrials.gov NCT02488109). This RCT compared HCR versus LCR in adolescents and young adults hospitalized with medical instability and malnutrition secondary to AN or atypical AN. Methods, primary short-term outcomes (Garber et al., 2021), and long-term outcomes (Golden et al., 2021) have been previously reported. Briefly, written informed consent was obtained from young adults and parents of minors, who provided written assent. Participants were enrolled at two clinical sites, large tertiary care children's hospitals with eating disorder inpatient programs attended by interdisciplinary Adolescent Medicine care teams at the University of California San Francisco and Stanford University, and randomized to HCR or LCR (see below). Data were collected prospectively, every day from hospital admission until discharge. The Institutional Review Board at each site approved the study.

2.2 | Participants

A modified intent-to-treat (mITT) approach (Dossing et al., 2016) included the 111 randomized participants who received treatment for at least 1 day out of the total 120 enrolled. Inclusion criteria were age 12–24 years old, admitted to hospital per Society for Adolescent Health and Medicine guidelines (Society for Adolescent Medicine, 2015) with AN or atypical AN, and >60%mBMI defined as 50th percentile BMI for age and sex (Centers for Disease Control, 2000). Median BMI > 85% was used to define atypical AN. AN and atypical AN diagnoses were made upon initial evaluation at admission using extensive growth history information from the electronic medical record; if diagnoses were already established, they were verified and documented. No patients with atypical AN had a prior history of AN, including AN with partial weight restoration. Exclusion criteria were hospital admission for malnutrition in the previous 6 months, currently pregnant or diagnosed with Bulimia Nervosa or Avoidant and Restrictive Food Intake Disorder, chronic disease, suicidality, or psychosis.

2.3 | Refeeding protocols

LCR began with 1400 kcal/day and increased by 200 kcal every other day; HCR commenced at 2000 kcal/day and increased by 200 kcal/day. Diets were prescribed by study physicians and increased per protocol until individual caloric goals were met based on Estimated Energy Requirement equations (Institute of Medicine, 2006) using height, age, and treatment goal weight. Our refeeding approach included three meals and 2–3

snacks per day (approximately 30–40% fat, 15–25% protein and 35–55% carbohydrate), with a hospital staff monitor during meals and 30–45 min afterward. At every meal, the percentage of every item consumed (e.g., proportion of sandwich, proportion of milk) was evaluated. Calories not voluntarily consumed in food were replaced by a high-energy oral liquid formula providing 1.50 kcal/mL; no participants received nasogastric (tube) feeding. All participants received a daily adult multivitamin with minerals and 500 mg elemental calcium twice per day. For the present analysis, a caloric "dose" was calculated by dividing the starting calorie level of the refeeding treatment for each participant (1400 kcal for LCR or 2000 kcal for HCR) by their individual baseline body weight in kilograms.

2.4 | Weight, vital signs, and laboratory data

Beginning at hospital admission, weight was measured daily on an electronic mobile stand-on scale, in the morning, post-voiding, before breakfast, and in gown only. Height was measured once at intake on a wall-mounted stadiometer. Percent mBMI was calculated as BMI (in kg/m^2 using daily weight and baseline height) divided by mBMI and multiplied by 100. Weight gain during hospitalization was calculated as total change in kg and %mBMI from hospital day one until discharge, and as a rate of gain (total %mBMI gain/length of stay in days). Heart rate (HR) was measured with continuous cardiac monitoring; postural changes of HR and blood pressure (BP) were assessed at least twice per day, with supine measurements (after 5 min rest), followed by standing measures (after 2 min). When multiple measures were taken within 24 h, the most deviant value (e.g., lowest BP) was recorded. Blood was drawn once by venipuncture between 5:00–7:00 am; samples were analyzed at the clinical laboratories of each institution.

The main efficacy outcome from the parent trial, time to restore medical stability, served as the primary outcome for the present study. This metric was adjudicated by a 6-point clinical index: (1) 24-h HR ≥45 bpm, (2) systolic blood pressure (SBP) ≥ 90 mmHg, (3) temperature ≥ 35.6°C, (4) orthostatic increase in HR ≤35 bpm, (5) orthostatic decrease in SBP ≤20 mmHg, and (6) ≥75%mBMI. Thresholds for these indicators represent the reversal of published vital sign instabilities supporting hospitalization in adolescents and young adults with eating disorders (Society for Adolescent Medicine, 2015). Criteria were assessed daily; medical stability was considered restored when at least four of six criteria were measured and deemed stable for 24 h. Other related outcomes were time to restore HR (as defined above), proportion in each group achieving medical and HR stability, weight gain, and length of hospital stay.

2.5 | Electrolyte abnormalities

Laboratory outcomes included the proportion of participants in each group with an electrolyte abnormality, proportion requiring electrolyte supplementation, and time to reach electrolyte nadir. The protocol for electrolyte monitoring and replacement is published (Garber et al., 2021). Serum electrolytes were monitored daily and repleted orally if below pre-determined thresholds. Electrolyte abnormalities present at the time of hospitalization were treated per protocol and rechecked and confirmed to be within normal limits prior to the onset of the refeeding intervention. Therefore, the hypophosphatemia (<3.0 mg/dL),

hypomagnesemia (<1.8 mg/dL), and hypokalemia (<3.5 mmol/L) reported here represent the incidence of abnormalities arising during treatment (after one full day of refeeding).

2.6 | Statistical analyses

The main outcome, time to restore medical stability, was compared among four groups over time, by diagnosis (AN and atypical AN) and refeeding treatment (HCR and LCR), with survival analysis using a log rank test, which does not assume proportional hazards. Those who did not reach the medical stability before hospital discharge were censored; analyses accounted for the site effect by stratification. Secondary treatment outcomes were HR, weight gain [kg, %mBMI and rate (%mBMI/day)], length of stay and initial weight change (kg and %mBMI). These secondary outcomes were compared first by diagnosis (AN vs. atypical AN) using independent t-tests of group means and Chi-squared or Fisher's exact tests for proportions. Secondary outcomes were then described across four groups, by diagnosis and refeeding treatment. Exploratory moderator analyses examined the interaction between diagnosis (AN or atypical AN) and treatment (LCR or HCR) on outcomes. This involved multivariable models including treatment (categorical variable HCR or LCR), diagnosis (categorical variable atypical AN or AN) and the interaction between treatment and diagnosis as independent variables and clinical outcomes as dependent variables. The effect of caloric dose (independent variable, kcal/kg) on treatment outcomes (dependent variables) was examined with unadjusted linear regressions. Analyses were performed using STATA version 16.1 (StataCorp, College Station, TX); significance was determined at alpha .05.

3 | RESULTS

3.1 | Participant characteristics

StRONG participants have been previously described in detail and compared by diagnosis at baseline among $n = 116$ (120 enrolled minus 4 post-randomization withdrawals). Briefly, participants with atypical AN and AN did not differ at baseline on key characteristics: they were 16.4 ± 2.5 years old on average, 91% female, predominantly non-Hispanic White (59%), 12% Asian, 21% Hispanic or Latino; and they presented with 21% loss of body mass, consistent with severe malnutrition (Society for Adolescent & Medicine, 2022). There was also no difference in illness severity between those with atypical AN versus AN (vital sign or laboratory value abnormalities) (Garber et al., 2019). The most common medical instabilities on admission were bradycardia (93%), hypotension (30%), and orthostatic increase in HR (60%). Mean electrolytes were within normal limits at baseline; however, a small percentage presented with electrolyte abnormalities that were treated prior to the initiation of the refeeding treatment: hypokalemia was most common (14%), followed by hypomagnesemia (4%) and hypophosphatemia (6%). Weight differed as expected by diagnosis: patients with atypical AN presented with significantly higher historical weight than those with AN. Participant flow through the trial has also been reported, with $n = 5$ withdrawals (2 with atypical AN and 3 with AN) after randomization and before receiving any treatment, leaving a final study mITT population of $n = 111$ (Garber et al., 2021).

3.2 | Treatment and outcomes by diagnosis

As shown in Table 1, 43% of the study population was diagnosed with atypical AN. Among those participants, 44% were randomized to HCR; among those with AN, 62% were randomized to HCR. Starting caloric dose (kcal/kg) was lower in the atypical AN group, by nature of their larger body weight, as compared to those with AN (32 kcal/kg vs. 43 kcal/kg, $p < .001$). There was no difference in the percentage who achieved medical stability in the atypical versus AN groups (87.3 vs. 81.3, $p = .38$). HR required 2.2 days longer to restore in those with atypical AN than AN ($p = .008$). Participants with atypical AN gained less weight than those with AN, whether expressed as kg, change in %mBMI, or rate of gain (%mBMI/day). A greater proportion of the atypical AN group developed hypomagnesemia ($p = .03$) and required magnesium supplementation during refeeding ($p = .01$); there were no differences in the occurrence of hypophosphatemia and hypokalemia, or correction of these electrolytes (p-values >.05).

3.3 | Effect of diagnosis by treatment interaction on outcomes

Figure 1 shows the main study outcome: the effect of HCR on time to restore medical stability, which was significantly different among the four groups (median restore time: HCR-AN 7 days, HCR-atypical AN 11 days, LCR-AN 10 days, LCR-atypical AN 10 days, logrank $p = .009$). Table 2 describes the study sample in four groups by diagnosis and refeeding treatment. Starting caloric dose was highest among those with AN on HCR (49 kcal/kg) and lowest in those with atypical AN on LCR (28 kcal/kg). Dosage for participants with atypical AN on HCR (38 kcal/kg) was similar to those with AN on LCR (34 kcal/kg). Medical stability was restored earliest among those with AN refed by HCR (7.1 ± 5.4 days), whereas those with atypical AN on HCR required 9.2 ± 5.0 days and were indistinguishable from the LCR groups with atypical AN and AN (10.7 ± 5.5 and 10.8 ± 5.2 days, respectively). Time to restore HR was shortest in those with AN on HCR (4.2 ± 3.4) and similar among the other three groups. Overall weight gain was lowest in those with atypical AN on LCR (1.3%mBMI) and did not appear different among the three other groups, however *rate* of weight gain suggested a dose–response pattern, whereby rate of gain decreased across the groups from higher to lower caloric dose. Relevant to safety, participants with atypical AN on LCR had the highest rates of hypomagnesemia. Time to serum nadir of phosphorus, magnesium and potassium appeared to follow a dose–response pattern whereby time to the lowest serum level increased across groups from higher to lower caloric dose.

Table 2 shows β (CI) and p-values from multivariate models exploring the interaction of diagnosis and treatment on refeeding outcomes. Although HCR improved overall weight gain in those with atypical AN by 3.9%mBMI, rate of weight gain was not faster and HR recovery was 3.8 days slower than those with AN refed by HCR. These interactions are illustrated in Figure 2. Panel (a) illustrates the interaction of diagnosis and HCR on HR recovery: HCR significantly shortens the time to HR recovery in participants with AN, however there is no effect in those with atypical AN. Panel (b) shows the effect on weight gain: participants with atypical AN gained significantly more weight if treated with HCR than LCR, whereas those with AN gained similar weight on either treatment.

The range of caloric doses received by the study participants was wide (22–71 kcal/kg). The average difference in caloric dose between participants with AN on HCR and those with atypical AN on HCR was approximately 10 kcal/kg. Therefore, we used regression models to examine the effect of a 10 kcal/kg increase in refeeding dose and found that it would significantly improve all outcomes. As shown in Table 3, for every 10 kcal/kg increase, time to medical stability shortened by −1.4 (−2.4, −.43) days ($p = .005$) and rate of weight gain increased by .17 (.12, .22)%mBMI, (<.001). In terms of safety, increasing caloric dose was associated with decreased incidence of hypomagnesemia [−.7 (−1.3, −.12), $p = .02$] and ~.7 day earlier nadir of all electrolytes (all $p < .05$).

4 | DISCUSSION

Patients hospitalized with malnutrition secondary to atypical AN required two additional days to restore medical stability and gained less weight in hospital than those with AN. These poor outcomes were due to an interaction between diagnosis and refeeding protocol. In other words, even when treated with HCR, a suboptimal caloric dose contributed to underfeeding in participants with atypical AN. The parent StRONG trial demonstrated the efficacy of HCR as compared to LCR to restore medical stability 3 days earlier, with no increase in electrolyte abnormalities, and savings of nearly USD 20,000 in healthcare charges per participant (Garber et al., 2021). Follow-up over year showed no difference in clinical remission or hospital readmission, thus maintaining the initial benefit of HCR (Golden et al., 2021). Extending this prior work, the present study shows that the superior efficacy of HCR in the StRONG trial (Garber et al., 2021) was driven by better outcomes in patients with AN, the population for whom the refeeding recommendations were intended. On the contrary, participants with atypical AN had protracted medical instability and poorer weight gain even when treated with HCR.

Time to medical stability did not differ by diagnosis alone. However, it was significantly different when compared over time among four groups (by diagnosis and treatment), showing that those with AN refed by HCR restored medical stability significantly faster. The lack of difference in time to medical stability by diagnosis alone may be because one of six criteria in our multifactorial medical stability index is restoration of %mBMI to 75%. Since this criterion was exceeded at baseline by all participants with atypical AN, the medical stability index may have been less sensitive for detecting differences by diagnostic group alone. However, bradycardia is the primary component of medical instability: 93% of participants in this trial had HR < 45 bpm during their first night in hospital. When comparing time to restore HR rate by diagnosis, it was clear that participants with atypical AN had delayed restoration. In exploratory analyses, we found that diagnosis interacted with treatment to delay heart recovery by 3.8 days. In other words, diagnosis of atypical AN weakens the effect of HCR on HR recovery.

Another notable difference by diagnostic group was that the incidence of hypomagnesemia was more than doubled in participants with atypical AN as compared to those with AN. The present study was based on data from a parent trial and therefore not powered to examine electrolyte abnormalities among four groups by diagnosis and treatment. However, when we examined refeeding dose as a predictor of outcomes, we found that higher calorie dose was

associated with *lower* incidence of refeeding hypomagnesemia. This same association was also observed in the parent StRONG trial, where the incidence of hypomagnesemia was half in participants treated with HCR (Garber et al., 2021). Thus, participants in both studies who were receiving the *lower* caloric treatments/dosages had more frequent magnesium abnormalities during longer periods of medical instability. These findings suggest that hypomagnesemia in these cases may be related to underfeeding, an interpretation that underscores the need to adopt higher calorie approaches into clinical practice when feasible.

Our findings do not suggest that there is something inherently different about individuals with atypical AN that results in worse outcomes in hospital. Rather, we found evidence that diagnosis of atypical AN interacted with treatment to diminish the effect of HCR. The interaction term between diagnosis and refeeding treatment can be expressed as caloric dose (kcal/kg body weight). These data indicate that 49 kcal/kg (the dose received by patients with AN on HCR) produced the best treatment outcomes, leading to significantly faster restoration of medical stability (3.7 days earlier) and HR (3.8 days earlier), and faster weight gain (.2%mBMI/day). In contrast, LCR provided participants with a low dose regardless of diagnosis (i.e., only 28 kcal/kg for participants with atypical AN, similar to the 34 kcal/kg dose for participants with AN). Selected past recommendations for LCR were expressed in kcal/kg; as low as 5–20 kcal/kg in Europe (MARSIPAN Working Group, 2014) and 30–40 kcal/kg in the US (American Dietetic Association, 2006; American Psychiatric Association, 2000, 2006). Prior research has examined doses averaging 38 kcal/kg (30–48 kcal/kg) (O'Connor & Nicholls, 2013). However, the safety and efficacy of higher dosages during hospitalizations and outcomes during follow-up must be investigated in patients with atypical AN, including psychological safety. We previously examined the effect of refeeding on mealtime distress and, while we found no difference between LCR and HCR, mealtime distress did significantly increase in relation to caloric dose (Accurso et al., 2023).

The treatment outcomes presented here are highly interrelated and typically used interchangeably in clinical settings. However, a notable finding was that weight gain did not operate consistently across diagnoses. Participants with atypical AN gained less weight (.7 kg or 2.3%mBMI less) than those with AN. However, examining weight gain across the four groups (by treatment and diagnosis) clarified that this was attributable to poor weight gain in those with atypical AN treated with LCR, who gained 75% less than those with atypical AN on HCR. Indeed, HCR did improve weight gain in participants with atypical AN to a level similar to those with AN on HCR, however HR recovery in atypical AN still lagged behind by more than 2 days. This suggests that the 38 kcal/kg dose received by those with atypical AN on HCR enhanced weight gain but was still insufficient to support autonomic recovery. Indeed, we showed that for every 10 kcal/kg increase in caloric dose, HR could be restored 1.7 days faster. These findings reinforce the limitations of relying on weight as a tool to guide recovery in atypical AN. Heart rate was particularly sensitive across diagnoses, supporting it as a valuable metric in the hospital. However, not all patients present with bradycardia and it is usually resolved by the time of discharge. Other recovery benchmarks such as hormonal and metabolic markers are urgently needed to support recovery in patients with atypical AN as they transition from hospital to ambulatory care.

A considerable strength of the present study was that treatments were randomized, and data were collected in the context of a clinical trial. Nevertheless, we acknowledge several limitations. First, this was a secondary data analysis; the parent trial was not designed to examine differences by diagnosis. This limitation was particularly evident in the laboratory outcomes, which were too few to compare across diagnosis and refeeding treatment. In addition, the medical stability index designed for the parent trial includes %mBMI and therefore was not as sensitive in the atypical AN group, as discussed. Second, the parent trial was designed to compare lower- vs. higher- calorie feeding, not caloric dose. The concept of caloric dose is not new, however, to our knowledge, it has not been applied across eating disorder diagnoses. The moderation analyses reported here were exploratory due to limited sample size. In addition, while we focused on the effect of baseline caloric dose, the rate of advancement was faster for HCR (200 kcal/day) as compared to LCR (200 kcal every other day). This undoubtedly contributed to faster achievement of outcomes in the HCR group. Nevertheless, it does not impact our main finding, that patients with atypical AN showed signs of underfeeding, even on HCR. Our results lend support for the use of caloric dose to individualize refeeding treatments across patients with malnutrition secondary to restrictive eating disorders, who are presenting with increasingly diverse body sizes requiring tailored refeeding treatments. They apply to hospitalized patients in the United States, and cannot be generalized to other clinical settings and other countries where treatment goals are different than medical stabilization. Further, these findings are limited to adolescents and young adults, who are growing and have the highest caloric requirements of the life span; they may not be generalized to older adult populations. Finally, and most importantly, the safety of higher caloric doses and long-term efficacy must be examined prospectively in a randomized fashion.

5 | CONCLUSIONS

The present study makes clear that a “one-size-fits-all” approach to refeeding cannot meet the needs of the diverse individuals admitted to hospital with restrictive eating disorders. The new frontier of refeeding must reflect patient diversity and keep pace with the wider move toward personalized medicine. Virtually all other pediatric treatments consider weight, which is known to affect metabolic rate, bioavailability of nutrients and pharmacokinetics. Future studies are needed to examine the efficacy and safety of individualized refeeding strategies for patients with atypical AN, whereby calories are appropriately dosed to body weight.

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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”

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Public significance:

The StRONG trial previously demonstrated the efficacy and safety of higher calorie refeeding in patients with malnutrition due to restrictive eating disorders. Here we show that higher calorie refeeding contributes to underfeeding in patients with atypical anorexia nervosa, including poor weight gain and longer time to restore medical stability. These findings indicate these patients need more calories to support nutritional rehabilitation in hospital.

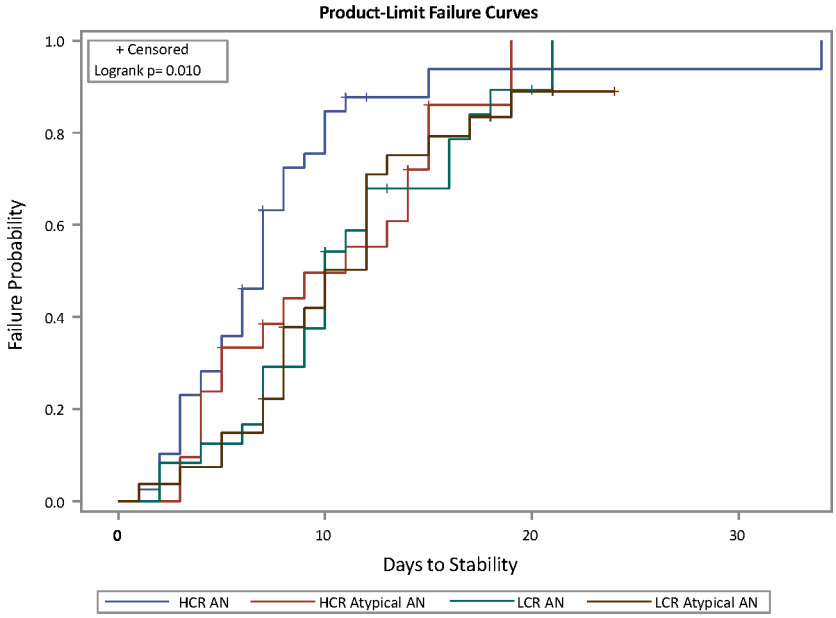

FIGURE 1.

Time to restore medical stability among patients with atypical AN and AN treated HCR or LCR. Participants with: HCR Atypical AN, atypical anorexia nervosa randomized to higher calorie refeeding; HCR AN, anorexia nervosa randomized to higher calorie refeeding; LCR Atypical AN, atypical anorexia nervosa randomized to lower calorie refeeding; LCR AN, anorexia nervosa randomized to lower calorie refeeding.

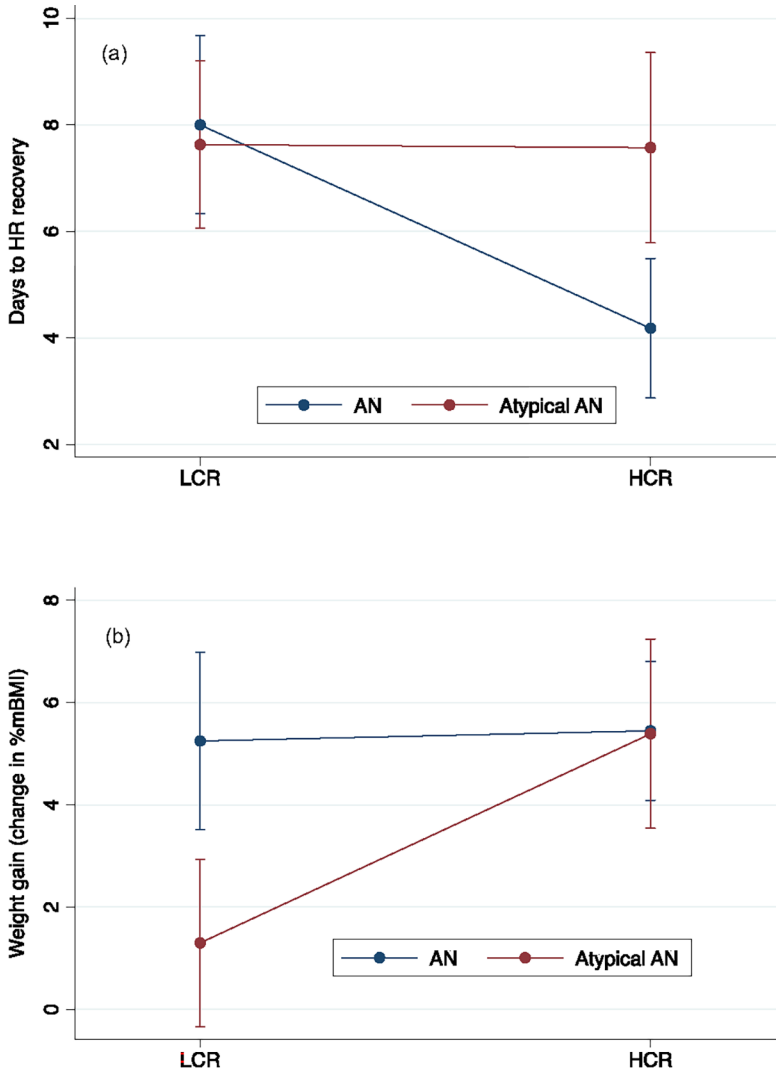

FIGURE 2.

Interaction between treatment (LCR or HCR) and diagnosis (AN or atypical AN) on days to restore heart rate (a) and overall weight gain (b). Panel (a) Interaction between treatment (LCR or HCR) and diagnosis (AN or atypical AN) on days to restore heart rate. Panel (b) Interaction between treatment (LCR or HCR) and diagnosis (AN or atypical AN) on overall weight gain.

TABLE 1

Comparison of refeeding treatments and outcomes by diagnosis.

	Atypical AN (*n* = 48)	AN (*n* = 63)	Difference (CI)	*p*-value	Effect size
Refeeding treatment					
% (No.) randomized to HCR[a]	44% (21)	62% (39)	18 (29, 58)	.057	NA
Admit refeeding dose (kcal/kg)[b]	32.4 ± 6.9	43.4 ± 9.8	11.0 (7.8, 14.3)	<.001	NA
Discharge refeeding dose (kcal/kg)[b]	53.3 ± 9.1	66.4 ± 12.0	13.1 (9.0, 17.3)	<.001	NA
Refeeding outcomes[a]					
Days to restore medical stability[c]	10.1 ± 5.3	8.5 ± 5.6	−1.6 (−3.7, .48)	.13	−.29
Days to restore heart rate[d]	8.7 ± 4.0	6.5 ± 3.9	−2.2 (−3.8, −.60)	.008	−.56
Weight gain (kg)	2.1 ± 1.7	2.9 ±2.5	.69 (.21, 1.3)	.007	.53
Weight gain (%mBMI)	3.1 ± 5.9	5.4 ± 2.9	2.3 (.6, 4.0)	.000	.51
Rate of gain (%mBMI/day)	.33 ± .40	.53 ± .22	.20 (.09, .32)	<.001	.66
Length of stay	11.1 ± 4.8	10.5 ± 5.4	−.64 (−2.6, 1.3)	.52	−.12
Initial weight Δ Day 1–2 (kg)	−.15 ± .68	.12 ± .42	.28 (.77, .49)	.008	.52
Initial weight Δ Day 1–2 (%mBMI)	−.16 ± .86	.24 ± .75	.40 (.96, .70)	.01	.50
Electrolyte abnormalities % (No.)[e]					
Hypophosphatemia (<3.0 mg/dL)	4% (2)	8% (5)	−4 (−12, 5)	.69	.50
Hypomagnesemia (<3.5 mmol/L)	29% (14)	11% (7)	−18 (−33, −3)	.03	3.29
Hypokalemia (<1.8 mg/dL)	10% (5)	5% (3)	−6 (−16, 4)	.29	2.32
Electrolyte correction % (No.)[e]					
Phosphate	4% (2)	10% (6)	5 (−2, 2)	.46	.41
Magnesium	31% (15)	11% (7)	−20 (−35, −5)	.01	3.64
Potassium	10% (5)	6% (4)	−4 (−14, 6)	.50	1.72
Day of electrolyte nadir[f]					
Phosphorus	5.3 ± 2.4	5.0 ± 2.1	−.30 (−1.16, .56)	.49	−.13
Magnesium	5.6 ± 3.0	5.6 ± 2.4	−.07 (−1.1, .94)	.88	−.03
Potassium	4.7 ± 3.1	4.1 ± 2.8	−.65 (−1.8, .46)	.25	−.22

Note: For data comparing group means, SD, group differences and confidence intervals (CI) are provided with *p*-values from unpaired *t*-tests and Cohen's d estimate of effect size: .2 (small effect); *d* = .5 (moderate effect); ≥.8 (large effect). For data comparing proportions, percent (number) in each group is provided with group differences, CI, *p*-values from Fisher's exact test (unless noted) and odds ratio to indicated effect size: 1.5 (small effect), 2 (medium effect), 3 (large effect).

Abbreviations: %mBMI, percent median body mass index; AN, anorexia nervosa; atypical AN, atypical anorexia nervosa; HCR, higher calorie refeeding; NA, not applicable indicates that effect sizes are not shown for baseline variables; OR, odds ratio.

[a]Percent and number in each group randomized to higher calorie refeeding, commencing with 2000 kcal/day and increasing by 200 kcal/day; *p*-value from chi-squared test.

[b]Refeeding treatment expressed as calories per kg body weight (kcal/kg).

[c]Days to restore to medical stability defined as: (1) 24-h heart rate (HR) ≥ 45 bpm, (2) systolic blood pressure (SBP) ≥ 90 mmHg, (3) temperature ≥ 35.6°C, (4) orthostatic increase in HR ≤35 bpm, (5) orthostatic decrease in SBP ≤20 mmHg, and (6) ≥75% of mBMI.

[d]Days to restore heart rate ≥ 45 bpm for 24 h in hospital, among *n* = 41 participants with atypical AN and *n* = 53 participants with AN with heart rate < 45 bpm on hospital day 1 (prior to beginning refeeding treatment).

[e]Percent and number in each group that developed electrolyte abnormalities and required electrolyte correction after initiation of refeeding treatment using standardized electrolyte correction protocol across clinical trial sites (Garber et al., 2021).

[f]Hospital day on which lowest serum electrolyte level was recorded.

TABLE 2

Baseline characteristics and refeeding outcomes among four groups, by diagnosis (atypical AN or AN) and treatment (LCR or HCR).

Baseline characteristics	**AN-HCR (*n* = 39)**	**Atypical AN-HCR (*n* = 21)**	**AN-LCR (*n* = 24)**	**Atypical AN-LCR (*n* = 27)**	***F***	***p*-value**
Refeeding dose (kcal/kg)[a]	49 ± 7	38 ± 5	34 ± 5	28 ± 3		
Weight (kg)	41.5 ± 5.4	53.2 ± 8.2	41.8 ± 5.3	51.4 ± 6.7	25.79	<.001
% mBMI	76.7 ± .06	95.6 ± .08	77.2 ± .06	95.0 ± .10	56.4	<.001
Heart rate (bpm)	42.7 ± 7.9	39.3 ± 4.1	40.4 ± 5.4	40.8 ± 4.5	1.66	.18
Systolic blood pressure (mmHg)	92 ± 7	98 ± 8	92 ± 8	95 ± 8	2.85	.04
Temperature (F)	36.6 ± .2	36.6 ± .2	36.6 ± .2	36.6 ± .2	.45	.72
Orthostatic Δ heart rate (bpm)	26 ± 11	29 ± 14	31 ± 14	27 ± 14	.66	.58
Orthostatic Δ blood pressure (mmHg)	.35 ± 6.0	1.1 ± 8.2	1.3 ± 6.0	.84 ± 9.1	.08	.96
Refeeding outcomes	**AN-HCR**	**Atypical AN-HCR**	**AN-LCR**	**Atypical AN-LCR**	**β (CI)**	***p*-value**
Days to medical stability[b]	7.1 ± 5.4	9.2 ± 5.0	10.8 ± 5.2	10.7 ± 5.5	2.2 (−1.9, 6.4)	.28
Days to restore heart rate[c]	4.2 ± 3.4	7.6 ± 4.6	8.0 ± 4.1	7.6 ± 4.7	3.8 (.57, 6.6)	.02
Weight gain (kg)	2.9 ± 1.7	2.8 ± 1.4	2.8 ± 1.2	1.6 ± 1.2	−1.2 (−2.3, .07)	.04
Weight gain (%mBMI)	5.4 ± 3.2	5.4 ± 2.5	5.2 ± 2.4	1.3 ± 7.1	−3.9 (−7.2, .59)	.02
Rate of gain (%mBMI/day)	.61 ± .21	.55 ± .31	.41 ± .19	.16 ± .38	−.19 (−.41, .02)	.08
Length of stay	9.0 ± 5.6	10.0 ± 4.6	13.0 ± 4.2	12 ± 4.8	2.0 (−1.8, 5.8)	.30

Note: Baseline characteristics presented as mean ± SD with *F*-statistic and *p*-value from one-way ANOVA comparison of means between the four groups (3 degrees of freedom). Refeeding outcomes presented as mean ± SD with beta coefficient (β), confidence interval (CI) and *p*-value from multivariate model with diagnosis, treatment and interaction between diagnosis and treatment as independent variables and refeeding outcome as dependent variable.

Abbreviations: %mBMI, percent median body mass index; AN, anorexia nervosa; atypical AN, atypical anorexia nervosa; HCR, higher calorie refeeding; LCR, low calorie refeeding; kcal/kg, calories per kilogram of body weight.

[a]Refeeding treatment expressed as calories per kg body weight (kcal/kg).

[b]Days to restore to medical stability defined as: (1) 24-h heart rate (HR) ≥ 45 bpm, (2) systolic blood pressure (SBP) ≥ 90 mmHg, (3) temperature ≥ 35.6°C, (4) orthostatic increase in HR ≤35 bpm, (5) orthostatic decrease in systolic BP ≤20 mmHg, and (6) ≥75% of mBMI.

[c]Days to restore heart rate > 45 bpm for 24 h in hospital, among $N = 41$ participants with atypical AN and $N = 53$ participants with AN with heart rate < 45 bpm on Day 1 (prior to beginning refeeding treatment).

TABLE 3

Effect of 10 kcal/kg increase in caloric dose on efficacy outcomes.

	β (CI)	*p*-value
Refeeding outcomes[a]		
Days to medical stability[c]	−1.4 (−2.4, −.43)	.005
Days to restore heart rate[d]	−1.7 (−2.5, −1.0)	<.001
Weight gain (kg)	.42 (.15, .69)	.002
Weight gain (%mBMI)	1.6 (.8, 2.4)	<.001
Rate of gain (%mBMI/day)	.17 (.12, .22)	<.001
Length of stay (days)	−1.2 (−2.1, −.34)	.008
Electrolyte abnormalities[b,e]		
Hypophosphatemia (<3.0 mg/dL)	.4 (−.3, 1.0)	.28
Hypomagnesemia (<3.5 mmol/L)	−.7 (−1.3, −.12)	.02
Hypokalemia (<1.8 mg/dL)	−.3 (−1.1, .5)	.46
Electrolyte correction[b,e]		
Phosphate	.5 (−.13, 1.2)	.12
Magnesium	−.5 (−1.0, .02)	.06
Potassium	−.1 (−.8, .6)	.78
Day of electrolyte nadir[a,f]		
Phosphorus	−.66 (−1.0, −.26)	.001
Magnesium	−.68 (−1.1, −.21)	.005
Potassium	−.68 (−1.2, −.15)	.012

Abbreviation: %mBMI, percent median body mass index.

[a]Beta coefficient (β), confidence interval (CI) and *p*-value come from multivariate model with caloric dose (kcal/kg body weight) as independent variable and refeeding outcomes or day of electrolyte nadir as dependent variable.

[b]Beta coefficient (β), confidence intervals (CI) and *p*-value from logistic regression with caloric dose (kcal/kg body weight) as independent variable and occurrence of electrolyte abnormalities and corrections (yes or no) as dependent variable.

[c]Days to restore to medical stability defined as: (1) 24-h heart rate (HR) ≥ 45 bpm, (2) systolic blood pressure (SBP) ≥ 90 mmHg, (3) temperature ≥ 35.6°C, (4) orthostatic increase in HR ≤35 bpm, (5) orthostatic decrease in SBP ≤20 mmHg, and (6) ≥75% of mBMI.

[d]Days to restore heart rate ≥ 45 bpm for 24 h in hospital, among $n = 41$ participants with atypical AN and $n = 53$ participants with AN with heart rate < 45 bpm on hospital day 1 (prior to beginning refeeding treatment).

[e]Percent and number in each group that developed electrolyte abnormalities and required electrolyte correction after initiation of refeeding treatment using standardized electrolyte correction protocol across clinical trial sites (Garber et al., 2021).

[f]Hospital day on which lowest serum electrolyte level was recorded.