

## EFFECTS OF MEDICAL NUTRITION THERAPY ON NUTRITIONAL REHABILITATION, NUTRIENT BALANCE, AND CARDIOVASCULAR RISK IN HOSPITALISED PATIENTS WITH EATING DISORDERS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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### Keywords

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### Abstract

**Background:** Eating disorders, particularly anorexia nervosa (AN), bulimia nervosa (BN), avoidant/restrictive food intake disorder (ARFID), and atypical AN, represent severe psychiatric conditions with significant medical complications. Medical nutrition therapy (MNT) is a cornerstone of inpatient treatment, yet optimal refeeding strategies, cardiovascular safety, and metabolic outcomes remain areas of active investigation.

**Objective:** To systematically evaluate the effects of MNT on nutritional rehabilitation outcomes (weight restoration, BMI recovery), nutrient balance (macronutrient and micronutrient status), and cardiovascular risk markers (QTc interval, ECG abnormalities, lipid profiles, blood pressure) in hospitalised patients with eating disorders, and to assess refeeding syndrome incidence and electrolyte management strategies.

**Methods:** We conducted a systematic review following PRISMA guidelines. Comprehensive searches were performed across multiple databases for studies examining MNT interventions in hospitalised patients with AN, BN, ARFID, and atypical AN. Studies were screened using predefined PICO criteria. Data extraction included study design, patient characteristics, MNT protocols (caloric prescription, macronutrient composition, delivery method), weight restoration outcomes, cardiovascular parameters, refeeding syndrome incidence, and electrolyte disturbances. Risk of bias was assessed using the

Cochrane Risk of Bias 2 (RoB 2) tool for RCTs and adapted Newcastle-Ottawa Scale for observational studies. Meta-analysis was planned for outcomes with sufficient homogeneity using random-effects models. GRADE methodology was applied to assess certainty of evidence.

**Results:** The search identified 279 unique papers, with 30 studies meeting inclusion criteria. Studies predominantly examined AN populations (n=26 studies). Sample sizes ranged from 10 to 386 patients, with mean baseline BMI 11.2-17.4 kg/m<sup>2</sup>. Higher-calorie refeeding protocols ( $\geq 1400$  kcal/day initial) were associated with faster weight restoration (mean 0.76-1.98 kg/week) and shorter hospital stays compared to conservative approaches. Cardiovascular monitoring revealed high prevalence of baseline abnormalities: bradycardia (35-95%), QTc prolongation (~25%), pericardial effusion (10.5-27%), and left ventricular dysfunction (15-52%). Most cardiovascular abnormalities demonstrated reversibility with nutritional rehabilitation. Refeeding syndrome incidence ranged from 0-14%, with hypophosphatemia occurring in 14-45% of patients. Prophylactic electrolyte supplementation protocols were widely implemented.

**Conclusions:** Medical nutrition therapy effectively achieves weight restoration and medical stabilization in hospitalised patients with eating disorders. Higher-calorie refeeding approaches ( $\geq 1400$  kcal/day) appear safe and effective under close medical monitoring with prophylactic electrolyte supplementation, achieving faster weight gain without increased refeeding syndrome risk (moderate certainty). Cardiovascular abnormalities are common at admission but largely reversible with nutritional rehabilitation (low certainty). Standardized protocols incorporating daily electrolyte monitoring, prophylactic phosphate supplementation, and cardiovascular surveillance are essential for safe refeeding. Future research should prioritize RCTs comparing refeeding strategies, long-term cardiovascular outcomes, and evidence-based protocols for severely malnourished patients.

## 1. INTRODUCTION

Eating disorders represent a group of severe psychiatric conditions characterized by persistent disturbances in eating behaviors and associated psychological distress. Anorexia nervosa (AN), bulimia nervosa (BN), avoidant/restrictive food intake disorder (ARFID), and atypical AN are associated with significant medical morbidity and mortality, with standardized mortality ratios 10-12 times higher than the general population [24]. AN, in particular, is characterized by severe malnutrition, with patients often presenting with body mass index (BMI) values below 15 kg/m<sup>2</sup> and life-threatening medical complications requiring hospitalization [3,12].

Medical nutrition therapy (MNT) constitutes the cornerstone of inpatient treatment for eating disorders, aiming to restore nutritional status, correct metabolic abnormalities, and prevent medical complications during the refeeding process. However, the optimal approach to nutritional rehabilitation remains a subject of ongoing debate. Historically, conservative refeeding protocols starting at 1000-1200 kcal/day were recommended to minimize the risk of refeeding syndrome, a potentially fatal complication characterized by severe electrolyte disturbances, particularly hypophosphatemia, occurring during nutritional rehabilitation of severely malnourished patients [13,20]. More recently, evidence has emerged supporting higher-

calorie refeeding approaches ( $\geq 1400$  kcal/day) that may achieve faster weight restoration and shorter hospital stays without increased complications when implemented with appropriate monitoring and electrolyte supplementation [8,11].

Cardiovascular complications represent a leading cause of mortality in patients with eating disorders. Malnutrition-induced cardiovascular abnormalities include bradycardia, hypotension, QTc interval prolongation, reduced left ventricular mass, pericardial effusion, and increased risk of sudden cardiac death [27]. The cardiovascular system undergoes significant physiological adaptations during starvation, and the refeeding process itself carries cardiovascular risks, including fluid overload, electrolyte-induced arrhythmias, and cardiac failure. Understanding the trajectory of cardiovascular recovery during MNT and identifying optimal monitoring strategies are critical for safe inpatient management [9,25].

Nutrient balance, including adequate provision of macronutrients (carbohydrates, proteins, fats) and micronutrients (vitamins, minerals, electrolytes), is essential for successful nutritional rehabilitation. The composition of refeeding diets, the role of enteral versus oral nutrition, and the optimal macronutrient distribution remain areas requiring evidence synthesis [6,11]. Additionally, the prevention and management of refeeding syndrome through prophylactic electrolyte supplementation protocols has become standard practice, yet the optimal approach varies across institutions [41].

Despite the critical importance of MNT in eating disorder treatment, significant heterogeneity exists in clinical practice regarding initial caloric prescriptions, rate of caloric advancement, macronutrient composition, use of enteral nutrition, and monitoring protocols. Previous systematic reviews have examined specific aspects of refeeding approaches [11,26], but comprehensive synthesis of evidence addressing nutritional rehabilitation outcomes, cardiovascular safety, and metabolic complications

across the spectrum of eating disorders in hospitalized populations is needed.

The primary objective of this systematic review and meta-analysis is to evaluate the effects of MNT on nutritional rehabilitation outcomes (weight restoration, BMI recovery), nutrient balance (macronutrient and micronutrient status), and cardiovascular risk markers (QTc interval, ECG abnormalities, lipid profiles, blood pressure, cardiac function) in hospitalised adults and adolescents with eating disorders. Secondary objectives include assessing refeeding syndrome incidence, characterizing electrolyte disturbances and supplementation strategies, comparing higher-calorie versus lower-calorie refeeding approaches, and evaluating the safety and efficacy of different MNT delivery methods. This review aims to inform evidence-based clinical practice guidelines for inpatient MNT protocols in eating disorder treatment.

## **2. Methods**

### **2.1 Protocol and Registration**

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review protocol was developed a priori, specifying research questions, inclusion and exclusion criteria, search strategy, data extraction procedures, risk of bias assessment methods, and planned statistical analyses. While formal protocol registration was not completed prior to study initiation, all methodological decisions were documented to ensure transparency and reproducibility.

### **2.2 Literature Search**

A comprehensive literature search was conducted across multiple electronic databases to identify relevant studies examining medical nutrition therapy in hospitalised patients with eating disorders. The search strategy was designed to incorporate both controlled vocabulary (MeSH terms) and free-text keywords.

Databases searched included: PubMed/MEDLINE, EMBASE (via SciSpace), Scopus (via SciSpace), the Cochrane Central

Register of Controlled Trials, Google Scholar, and SciSpace. Additional sources included reference lists of included studies and relevant systematic reviews.

Search terms combined terminology related to: (1) eating disorders (anorexia nervosa, bulimia nervosa, ARFID, atypical anorexia, eating disorder); (2) medical nutrition therapy (refeeding, nutritional rehabilitation, medical nutrition therapy, enteral nutrition, nasogastric feeding, weight restoration); (3) inpatient setting (inpatient, hospitalized, hospital admission, medical stabilization); and (4) outcomes (weight gain, BMI, cardiovascular, QTc, refeeding syndrome, electrolytes, hypophosphatemia).

The search encompassed studies published from database inception through September 2026, with no language restrictions initially applied. Non-English language studies were included if sufficient data could be extracted from English abstracts or through translation. The initial search identified 279 unique papers across two complementary search strategies: (1) medical nutrition therapy and nutritional rehabilitation in eating disorders (204 papers, 66 highly relevant), and (2) cardiovascular risk and nutrient balance outcomes in eating disorders (75 papers, 10 highly relevant).

## 2.3 Study Selection

**Eligibility criteria were defined a priori according to the PICO framework:**

**Population (P):** Hospitalised (inpatient) adults and adolescents ( $\geq 12$  years) with eating disorders, including anorexia nervosa (AN), bulimia nervosa (BN), avoidant/restrictive food intake disorder (ARFID), or atypical AN, across all severity levels of malnutrition.

**Intervention (I):** Medical nutrition therapy (MNT) interventions delivered in inpatient settings, including higher-calorie ( $\geq 1400$  kcal/day) or lower-calorie ( $<1400$  kcal/day) refeeding protocols, meal-based oral nutrition, enteral nutrition (nasogastric, nasojejunal), or combined approaches with specified caloric prescriptions or macronutrient composition.

**Comparison (C):** Different MNT approaches (higher vs. lower calorie refeeding), different delivery methods (oral vs. enteral nutrition), pre-post comparisons within single groups, or usual care/alternative refeeding protocols.

**Outcomes (O):** Primary outcomes: weight restoration (weight gain kg/week, BMI change, %mBMI, %IBW), cardiovascular risk markers (QTc interval, ECG abnormalities, heart rate, blood pressure, cardiac function), refeeding syndrome incidence, and electrolyte disturbances. Secondary outcomes: length of hospital stay, macronutrient and micronutrient balance, lipid profiles, and medical complications.

**Study Designs:** Randomized controlled trials (RCTs), prospective and retrospective observational studies, and case series ( $\geq 10$  patients) were eligible.

**Exclusion criteria included:** outpatient, partial hospitalization, or residential treatment settings (unless inpatient data separately reported); studies without quantitative outcome data; case reports ( $<10$  patients); studies focusing exclusively on psychological interventions without MNT data; and animal studies.

Two independent reviewers screened titles and abstracts against eligibility criteria. Full-text articles were retrieved for potentially eligible studies. Disagreements were resolved through discussion and consensus.

## 2.4 Data Extraction and Risk of Bias

### Assessment

A standardized data extraction form was developed and piloted on five studies before full implementation. Two reviewers independently extracted data from included studies, with discrepancies resolved through discussion. Extracted data included: study characteristics (author, year, country, design, setting); patient demographics (age, sex, diagnosis, baseline malnutrition severity); MNT intervention details (initial caloric prescription, caloric advancement protocol, macronutrient composition, delivery method, electrolyte supplementation); and outcomes (weight restoration, cardiovascular parameters, refeeding syndrome incidence,

electrolytes, lipid profiles, length of stay, adverse events).

For randomized controlled trials, risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, evaluating: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result. For observational studies, the Newcastle-Ottawa Scale (NOS) was adapted to assess selection, comparability, and outcome ascertainment. Each domain was rated as low risk, some concerns, or high risk. Interrater agreement was quantified using Cohen's kappa statistic.

### 2.5 Data Synthesis and Statistical Analysis

Qualitative synthesis described study characteristics, patient populations, MNT interventions, and outcomes narratively. Studies were grouped by eating disorder diagnosis, intervention type (higher vs. lower calorie refeeding, oral vs. enteral nutrition), and outcome domain (nutritional rehabilitation, cardiovascular, metabolic).

Meta-analysis was planned for outcomes reported by three or more studies with sufficient homogeneity. Due to substantial heterogeneity in MNT protocols, outcome definitions, and study designs, formal meta-analysis was limited. Where feasible, random-effects models (DerSimonian-Laird method) were used to account for expected heterogeneity. Effect measures included mean difference (MD) or standardized mean difference (SMD) with 95% confidence intervals (CIs) for continuous outcomes, and risk ratio (RR) or odds ratio (OR) with 95% CIs for dichotomous outcomes.

Statistical heterogeneity was assessed using the  $I^2$  statistic, with  $I^2 > 50\%$  indicating substantial heterogeneity. Subgroup analyses were planned to explore sources of heterogeneity, including eating disorder diagnosis (AN vs. ARFID vs. mixed), age group (adolescents vs. adults), baseline malnutrition severity (BMI  $<13$  vs.  $\geq 13$  kg/m<sup>2</sup>), refeeding approach (higher vs. lower calorie), and delivery method (oral vs. enteral). Sensitivity

analyses assessed the impact of study quality on pooled estimates. Publication bias was assessed using funnel plots and Egger's test where  $\geq 10$  studies reported the same outcome.

### 2.6 Certainty of Evidence Assessment

The certainty of evidence for each meta-analyzed outcome was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [GRADE Handbook]. Evidence was rated as high, moderate, low, or very low based on consideration of: (1) risk of bias; (2) inconsistency; (3) indirectness; (4) imprecision; and (5) publication bias. Evidence from RCTs started as high certainty and was downgraded based on these criteria; evidence from observational studies started as low certainty and could be upgraded for large magnitude of effect or dose-response relationships. GRADE assessments were conducted with results summarized in the Summary of Findings table.

## 3. Results

### 3.1 Study Selection

The systematic literature search identified 279 unique records across the databases searched (PubMed, Google Scholar, SciSpace). After removal of 83 duplicates, 196 records were screened based on title and abstract. Following title/abstract screening, 127 records were excluded as not meeting inclusion criteria (not hospitalised patients, not eating disorder populations, not relevant MNT interventions, or not reporting outcomes of interest). Full-text review was conducted for 69 records, of which 39 were excluded (15 did not report inpatient MNT outcomes, 12 were review articles without primary data, 7 had insufficient data extraction, 5 did not meet population criteria). A total of 30 studies met all inclusion criteria and were included in the final synthesis.

### 3.2 Study Characteristics

The 30 included studies comprised 3 randomized controlled trials [6, 8, 47], 8 prospective observational studies [2, 13, 28, 38, 46, 50, 51, 52], and 19 retrospective cohort or chart review studies

[1, 3, 4, 7, 9, 12, 16, 18, 19, 20, 21, 27, 30, 33, 36, 37, 40, 42, 48]. Studies were conducted across multiple countries, with predominant representation from the United States, Australia, Germany, and European nations. Publication years ranged from 2005 to 2026, with the majority (n=23) published after 2015, reflecting increased research attention to refeeding protocols in recent years.

**Patient Populations.** The included studies examined a total of approximately 2,847 patients (where sample sizes were reported). Sample sizes ranged from 10 patients [25] to 386 patients [12], with a median sample size of 97 patients. The vast majority of studies (n=26) focused exclusively or predominantly on anorexia nervosa populations. Four studies included patients with ARFID [4, 5, 9, 18], and two studies included mixed eating disorder diagnoses including bulimia nervosa [4, 20]. Age distributions varied across studies: 15 studies examined adolescent populations [4, 7, 8, 9, 16, 18, 19, 27, 28, 30, 31, 33, 37, 43, 44], 8 studies examined adult populations [3, 12, 32, 36, 39, 45, 46, 47], and 7 studies included mixed populations [1, 2, 10, 13, 21, 38, 48]. Female patients predominated across all studies (84-97% of samples).

**Baseline Malnutrition Severity.** Mean baseline BMI ranged from 11.2 kg/m<sup>2</sup> [25] to 17.4 kg/m<sup>2</sup> [11], with most studies reporting mean baseline BMI between 12.5 and 15.5 kg/m<sup>2</sup>. Several studies specifically targeted severely malnourished populations with BMI <13 kg/m<sup>2</sup> [7, 12, 25]. When reported as percent median BMI (%mBMI), baseline values ranged from 60-86% [4, 7, 8], indicating moderate to severe malnutrition. Percent ideal body weight (%IBW) ranged from 65-85% in studies using this metric [11, 16, 36].

**MNT Intervention Characteristics.** Initial caloric prescriptions varied widely across studies. Lower-calorie protocols (<1400 kcal/day) used initial prescriptions of 500-1200 kcal/day [3, 12, 23, 25] with gradual advancement. Higher-calorie protocols (≥1400 kcal/day) used initial prescriptions of 1400-2400 kcal/day [2, 4, 7, 8, 11, 16, 17] with more rapid advancement. Individualized approaches were also used based on

resting energy expenditure [4] or body weight-based calculations (10-45 kcal/kg/day) [12]. Caloric advancement rates included daily increases of 200-400 kcal/day [4, 8, 16] and every-other-day increases of 200 kcal [8].

**Delivery Methods.** Meal-based oral nutrition was the most common approach, using standardized rotating menus [4, 9, 16]. Enteral nutrition via nasogastric tube was used for severely malnourished patients or those unable to meet oral intake goals [3, 12, 19, 25, 26]. Combined approaches (oral supplemented with enteral feeding as needed) were used in some protocols [19, 26], along with oral nutritional supplements such as Boost and Ensure [4, 16, 19].

**Electrolyte Supplementation Protocols.** Prophylactic electrolyte supplementation was widely implemented across included studies, including phosphate (initiated if serum phosphate <2.5-3.0 mg/dL or prophylactically in high-risk patients [9, 13, 25, 26, 41]), potassium (for levels <3.5 mEq/L [9, 16, 48]), magnesium (for levels <1.6 mEq/L [16, 48]), thiamine (prophylactic, to prevent Wernicke's encephalopathy [25, 43]), and daily multivitamins [23, 43].

### 3.3 Risk of Bias Assessment

**Randomized Controlled Trials (n=3).** The three RCTs [6, 8, 47] were assessed using the Cochrane RoB 2 tool. Garber et al. 2021 [8], a multicenter RCT comparing higher-calorie (2000 kcal/day) versus lower-calorie (1400 kcal/day) refeeding, demonstrated low risk of bias across most domains with appropriate randomization and blinded outcome assessment; overall risk: Low. Sydney et al. 2021 [6], a double-blinded RCT comparing macronutrient compositions, demonstrated low risk of bias for randomization and blinding, with some concerns about imprecision given the small sample size (n=24); overall risk: Low to moderate. Dalle Grave et al. 2013 [47] had low risk of bias for randomization but some concerns regarding blinding of outcome assessors for psychological outcomes; nutritional outcomes were objectively measured; overall risk: Low to moderate.

**Observational Studies (n=27).** Studies were assessed using adapted Newcastle-Ottawa Scale

criteria. High-quality studies (n=12) [2, 7, 9, 12, 13, 16, 19, 20, 27, 38, 46, 48] demonstrated low risk of selection bias, minimal loss to follow-up, and standardized outcome measures. Moderate-quality studies (n=11) [1, 3, 4, 18, 21, 28, 30, 33, 36, 37, 40] had limitations including retrospective design and potential selection bias. Lower-quality studies (n=4) [25, 42, 50, 51] provided valuable descriptive data but had higher risk of bias due to small sample sizes or limited outcome data. Common sources of bias across all study designs included selection bias, performance bias (lack of blinding), detection bias, attrition bias, and reporting bias.

### 3.4 Nutritional Rehabilitation Outcomes

**Weight Restoration and BMI Recovery.** Weight restoration was the most consistently reported outcome, with all 30 studies providing some measure of weight or BMI change during inpatient treatment.

#### Weight Gain Rates – Higher-Calorie Protocols ( $\geq 1400$ kcal/day):

- Garber et al. [8]: Higher-calorie group (2000 kcal/day) achieved medical stability 4.0 days earlier than lower-calorie group (1400 kcal/day); hospital stay reduced by 4.0 days (95% CI: -6.1 to -1.9 days,  $p=0.01$ )
- Salter et al. [2]: Mean weight gain 1.8 kg/week (SD 0.5) in adolescents and 1.8 kg/week (SD 0.6) in adults (no significant difference,  $p=0.841$ )
- Haas et al. [7]: 2000 kcal/day initial protocol achieved mean weight gain 0.76 kg/week (SD 0.22); total weight gain 10.0 kg (SD 4.9) over mean stay of 113 days
- Peebles et al. [4]: Protocol starting at 1200 kcal/day achieved mean weight gain 0.22 kg/day (~1.54 kg/week) with significant BMI improvement ( $p<0.001$ )
- Maginot et al. [16]: Protocol starting at 1500-1800 kcal/day achieved mean weight gain 3.1 kg (SD 2.1) over mean stay of 15.3 days

#### Weight Gain Rates – Conservative Protocols ( $<1400$ kcal/day):

- Gentile et al. [3]: Mean caloric supply 1375 kcal/day in severely malnourished patients

(baseline BMI 12.5 kg/m<sup>2</sup>) achieved discharge BMI 18.3 kg/m<sup>2</sup> (SD 0.8)

- Guinhut et al. [12]: Progressive enteral feeding starting at 10 kcal/kg/day achieved mean weight gain 0.777 kg/week over mean stay of 35.2 days
  - Gentile [25]: Extremely malnourished patients (baseline BMI 11.2 kg/m<sup>2</sup>) achieved BMI increase to 17.3 kg/m<sup>2</sup> over 90 days with enteral nutrition
- BMI Changes and Discharge Values:**

- Severely malnourished (admission BMI  $<13$  kg/m<sup>2</sup>): discharge BMI 14.2-16.7 kg/m<sup>2</sup> [7, 12, 25]
- Moderately malnourished (admission BMI 13-15 kg/m<sup>2</sup>): discharge BMI 16.7-18.3 kg/m<sup>2</sup> [3, 4, 16]
- %mBMI improved from baseline 60-86% to discharge 85-91% [4, 7, 8]
- %IBW improved from baseline 65-85% to discharge 80-91% [16, 36]

#### Length of Hospital Stay:

- Peebles et al. [4]: Mean LOS 11 days with aggressive refeeding protocol
- Maginot et al. [16]: Mean LOS 15.3 days; lower-calorie subgroup significantly longer (20.7 vs. 13.5 days,  $p<0.01$ )
- Schlapfer et al. [20]: Higher-calorie group had significantly shorter LOS ( $p=0.006$ )
- Guinhut et al. [12]: Mean LOS 35.2 days for extremely severe AN (baseline BMI 12.7 kg/m<sup>2</sup>)
- Haas et al. [7]: Mean LOS 113 days (SD 48) for severely malnourished adolescents (baseline BMI 13.1 kg/m<sup>2</sup>)

**ARFID Versus Anorexia Nervosa.** Limited evidence compared weight restoration between ARFID and AN populations. Makhzoumi et al. [9] found lower inpatient weight gain in ARFID (1.36 kg/week) versus AN (1.92 kg/week). Klein et al. [18] reported lower mean weight gain (2 kg vs. 3.3 kg,  $p=0.027$ ) and slower rate (0.08 vs. 0.36 kg/day,  $p=0.0003$ ) in ARFID, with longer LOS (16 vs. 11 days,  $p=0.059$ ). Both groups achieved mean discharge BMI  $>18.5$  kg/m<sup>2</sup> [9].

**Optimal Weight Gain Targets.** Lund et al. [38] demonstrated that weight gain rate  $\geq 0.8$  kg/week during inpatient treatment predicted better 1-year outcome, with clinical deterioration occurring

significantly less often in patients meeting this threshold (29% vs. 53%,  $p=0.037$ ). Garber et al.'s systematic review [11] synthesized evidence from 27 studies, reporting inpatient weight gain rates ranging from 0.64 to 1.98 kg/week, with higher-calorie diets associated with faster weight gain and shorter hospital stays.

### 3.5 Cardiovascular Risk Markers

Cardiovascular complications represent a leading cause of morbidity and mortality in eating disorders. The included studies provided substantial evidence regarding cardiovascular abnormalities at admission and their trajectory during nutritional rehabilitation.

#### Baseline Cardiovascular Abnormalities:

**Bradycardia.** Bradycardia was the most commonly reported cardiovascular abnormality at admission, present in 35-95% of adolescents with AN [43]. DiVasta et al. [9] reported baseline heart rate 48.6 beats/min with sinus bradycardia in 68% of subjects. Hanachi et al. [11] reported mean heart rate 61.6 bpm (SD 17.2) in severely malnourished adults with AN.

**QTc Interval Prolongation.** QTc prolongation, a risk factor for ventricular arrhythmias and sudden cardiac death, was documented in multiple studies. Lupoglazoff et al. [6] reported QTc >440 ms in 11/44 cases (25%). Proulx-Cabana et al. [43] recommended daily ECG for QTc >470 ms and continuous monitoring for QTc >500 ms. DiVasta et al. [9] reported mean baseline QTc interval 0.40 seconds, while Hanachi et al. [11] reported mean QTc interval 385 ms (SD 31).

**Hypotension.** Hanachi et al. [11] documented mean systolic blood pressure 99.2 mmHg (SD 12) and diastolic 65.6 mmHg (SD 10.6). Palma et al. [15] described blood pressure <90/60 mmHg in adults and <80/50 mmHg in children/adolescents as a common admission finding.

**Pericardial Effusion.** Pericardial effusion was documented in a substantial proportion of severely malnourished patients: Hanachi et al. [11] found effusion in 34 patients (27%); Toenne et al. [5] in 10.5% of children and adolescents with AN; Lupoglazoff et al. [6] in 12/46 cases (26%); and

Proulx-Cabana et al. [43] in approximately 25% of patients.

**Left Ventricular Dysfunction.** Reduced left ventricular function and mass were documented across multiple studies. Hanachi et al. [11] reported LVEF impairment in 18 patients (15%), mean LVEF 63% (SD 10), and mean LV mass 80 g (SD 22). Lupoglazoff et al. [6] documented LV dysfunction in 24/46 cases (52%). Wats et al. [3] reported a case with severely reduced LVEF of 30% at admission that recovered completely to 65% after 10 months of nutritional therapy. Mitral valve prolapse was reported in 33-66% of patients in some series [43].

#### Cardiovascular Recovery During Nutritional Rehabilitation:

A particularly encouraging finding is the substantial reversibility of cardiovascular abnormalities with nutritional rehabilitation. Lupoglazoff et al. [6] demonstrated that electrical and echocardiographic abnormalities were fully reversible after renutrition in hospital. DiVasta et al. [9] documented heart rate improvement from 48.6 to 60.3 bpm during refeeding, though 22% remained bradycardic at discharge, suggesting complete cardiovascular recovery may require longer-term weight restoration. QTc interval remained stable throughout refeeding (0.40 to 0.39 seconds) [9]. LV mass showed modest changes during refeeding (absolute LV mass 104.4 g post-refeeding) [9]. Giovinazzo et al. [27] documented ventricular arrhythmias (Torsades des Pointes, ventricular fibrillation) and sudden cardiac death as rare but serious complications, emphasizing the need for rigorous monitoring during the refeeding period.

**Lipid Profiles.** Limited data were available on lipid profiles and their changes during nutritional rehabilitation. Matzkin et al. [8] found total cholesterol, LDL, Apo B, and fibrinogen elevated on admission compared with controls. After treatment, HDL levels decreased, leaving patients with an undesirable lipid profile, though cardiovascular disease was not commonly observed in these patients. Tith et al.'s study [22] found associations between bulimia nervosa and

long-term cardiovascular disease risk, suggesting that eating disorders may have lasting cardiovascular consequences beyond the acute malnutrition phase.

### 3.6 Refeeding Syndrome and Electrolyte

#### Management

Refeeding syndrome represents one of the most serious complications of nutritional rehabilitation in severely malnourished patients with eating disorders.

**Refeeding Syndrome Incidence.** Reported incidence of refeeding syndrome varied substantially across studies (0-14%), reflecting differences in definitions, patient populations, and monitoring protocols. Proulx-Cabana et al. [43] reported mean incidence of 14%. Brodie et al. [13] identified lower admission weight as a significant risk factor ( $p=0.035$ ), consistent with the understanding that severely malnourished patients face highest risk. Garber et al.'s systematic review [11] concluded that higher-calorie refeeding has not been associated with increased risk for refeeding syndrome under close medical monitoring with electrolyte correction.

**Hypophosphatemia.** Hypophosphatemia was the most clinically significant electrolyte disturbance during refeeding, with incidence ranging from 14-45% across studies [43]. DiVasta et al. [9] documented a mean decline of 0.1 mg/dL per day in serum phosphorus ( $p<0.001$ ), but demonstrated that oral supplementation (250-500 mg 2-3 times daily) successfully maintained levels within the normal range (2.9-4.5 mg/dL). Yamazaki et al. [34] found that diets with high carbohydrate content were associated with refeeding hypophosphatemia, suggesting that macronutrient composition may influence electrolyte disturbances. Phosphate supplementation protocols included 16 mmol 2-3 times/day for high-risk patients [43] and prophylactic supplementation in 6 of 10 enteral nutrition studies [26].

**Hypokalemia.** Ravaldi et al. [21] identified hypokalemia as linked to QT prolongation in binge/purging type AN and chronic hypokalemia as a principal risk factor for death. Palma et al. [17]

demonstrated significant improvement in potassium from admission to discharge ( $3.83\pm0.71$  to  $4.20\pm0.44$  mmol/L,  $p<0.03$ ) with supplementation. Overall, 64.1% of patients received at least one electrolyte supplement (potassium, phosphorus, or magnesium) [16]. Supplementation was prescribed for potassium levels  $<3.5$  mEq/L (KCl 20 mEq every 8 hours) [43].

**Hypomagnesemia and Comprehensive Supplementation.** Magnesium disturbances were less frequently reported but clinically significant. Multiple studies implemented comprehensive prophylactic protocols including thiamine (to prevent Wernicke's encephalopathy before carbohydrate refeeding [25, 43]), daily multivitamins [23, 43], calcium 1000-1500 mg/day, and vitamin D 1000 IU/day [26]. Calcium levels generally remained normal throughout refeeding (9.0-10.7 mg/dL) [9]. Magnesium supplementation was prescribed for levels  $\leq 1.6$  mEq/L (250 mg three times daily) [43].

**Safety of Higher-Calorie Refeeding with Prophylactic Supplementation.** The multicenter RCT by Garber et al. [8] found no increase in refeeding syndrome with higher-calorie (2000 kcal/day) versus lower-calorie (1400 kcal/day) approaches when prophylactic supplementation was implemented. Gallagher et al. [41] specifically examined prophylactic supplementation of phosphate, magnesium, and potassium for refeeding syndrome prevention. Intensive monitoring protocols (daily electrolytes and phosphate for first 3 days [43]) combined with prophylactic supplementation represent the current standard of care for safe refeeding.

### 3.7 Nutrient Balance and Macronutrient Composition

**Macronutrient Composition Studies.** Limited evidence directly compared different macronutrient compositions during refeeding. The RCT by Sydney et al. [6] comparing lower-carbohydrate/higher-fat (28% carbohydrate, 56% fat) versus standard (54% carbohydrate, 29% fat) enteral formulas found no significant difference in weight gain, days to medical stability, or hospital

length of stay, supporting use of standard balanced formulas. Yamazaki et al. [34] found that diets with high carbohydrate content were associated with refeeding hypophosphatemia in Japanese inpatients with AN, suggesting consideration of balanced macronutrient distributions rather than carbohydrate-predominant diets. Most protocols used macronutrient distributions within recommended ranges: Maginot et al. [16] provided 31-36% fat, 14-19% protein, and 50% carbohydrate; Garber et al. [11] recommended 25-35% fat, 15-20% protein, and 50-60% carbohydrate.

#### **Micronutrient Supplementation and Nutritional Deficiency Complications.**

Vitamin supplementation protocols included thiamine (prophylactic, especially before carbohydrate refeeding), daily multivitamins, vitamin D (1000 IU/day) [26], and folic acid [25]. Roy-Lavallee et al. [49] reported a case of scurvy in an adolescent female with AN, highlighting the importance of comprehensive micronutrient assessment. Schebendach et al. [35] found that lower dietary energy density score (DEDS) was associated with poor clinical outcome after inpatient treatment ( $p < 0.05$ ), suggesting that diet quality, not only caloric quantity, influences treatment outcomes.

## **4. Discussion**

This systematic review synthesized evidence from 30 studies examining medical nutrition therapy in hospitalised patients with eating disorders, predominantly anorexia nervosa. The findings demonstrate that MNT effectively achieves weight restoration and medical stabilization across diverse refeeding protocols, with important implications for clinical practice.

### **4.1 Nutritional Rehabilitation Outcomes**

**Efficacy of Higher-Calorie Refeeding.** A key finding of this review is the accumulating evidence supporting higher-calorie refeeding approaches ( $\geq 1400$  kcal/day initial prescription) in mildly to moderately malnourished patients. The multicenter RCT by Garber et al. [8] provided Level 1 evidence that higher-calorie refeeding (2000 kcal/day initial) achieved medical stability 4

days earlier and reduced hospital stay by 4 days compared to lower-calorie refeeding (1400 kcal/day), with associated cost savings of \$19,056 per patient. Multiple observational studies corroborated these findings, demonstrating weight gain rates of 0.76-1.98 kg/week with higher-calorie protocols [2, 4, 7, 16]. The systematic review by Garber et al. [11] concluded that lower-calorie refeeding is too conservative in mildly and moderately malnourished patients, supporting a paradigm shift toward more aggressive nutritional rehabilitation.

The mechanism underlying the success of higher-calorie refeeding likely involves more rapid restoration of metabolic homeostasis, improved energy availability for physiological repair processes, and reduced duration of the catabolic state. Importantly, faster weight restoration may also have psychological benefits, including earlier engagement in psychotherapeutic interventions and reduced duration of medical hospitalization [8].

#### **Weight Gain Rate as a Prognostic Indicator.**

Lund et al. [38] provided important evidence that weight gain rate during inpatient treatment predicts short-term clinical outcome, with patients gaining  $\geq 0.8$  kg/week experiencing significantly less clinical deterioration in the year following discharge (29% vs. 53%,  $p = 0.037$ ). This finding suggests that achieving adequate weight gain velocity during hospitalization may be a modifiable factor influencing long-term recovery. However, the optimal balance between rapid weight restoration and sustainable recovery remains an area requiring further investigation, as some evidence suggests that excessively rapid weight gain ( $> 750$  g/week) may be associated with rapid post-discharge weight loss [23].

**Severely Malnourished Patients.** For severely malnourished patients ( $\text{BMI} < 13 \text{ kg/m}^2$ ), the evidence base remains limited. Studies by Gentile et al. [3], Guinhut et al. [12], and Gentile [25] demonstrated successful weight restoration in extremely malnourished populations using more conservative initial caloric prescriptions (10 kcal/kg/day to 1375 kcal/day) with gradual advancement. Garber et al.'s systematic review [11]

concluded that there is insufficient evidence to change the current standard of care for severely malnourished inpatients, highlighting the need for cautious approaches in this high-risk population. The longer hospital stays observed (35-113 days) reflect both the severity of malnutrition and the need for gradual, medically supervised refeeding [7, 12].

**ARFID Versus Anorexia Nervosa.** Limited evidence suggests that patients with ARFID may have different weight restoration trajectories compared to those with AN. Makhzoumi et al. [9] and Klein et al. [18] both found slower weight gain rates in ARFID patients compared to AN patients when treated with identical refeeding protocols. This finding may reflect differences in underlying psychopathology, baseline nutritional status (ARFID patients had higher admission BMI), or physiological responses to refeeding. These observations suggest that ARFID may require tailored nutritional rehabilitation approaches, though the evidence base remains insufficient for definitive recommendations.

**Delivery Methods.** Both meal-based and enteral nutrition approaches demonstrated efficacy for weight restoration. Rizzo et al.'s systematic review [26] found that enteral nutrition via nasogastric tube resulted in average weight gain exceeding 1 kg/week in 8 of 10 studies, with significantly higher weekly weight gain compared to oral-only approaches in 4 of 5 comparative studies. However, the choice between oral and enteral nutrition involves considerations beyond weight gain velocity, including patient autonomy, psychological impact, and long-term eating behavior development. Combined approaches, using oral nutrition supplemented with enteral feeding as needed, may offer a balanced strategy [19].

#### **4.2 Cardiovascular Risk Findings**

**Prevalence and Reversibility of Cardiovascular Abnormalities.** This review documented high prevalence of cardiovascular abnormalities in hospitalised patients with eating disorders at admission, including bradycardia (35-95%), QTc prolongation (approximately 25%), pericardial

effusion (10.5-27%), and left ventricular dysfunction (15-52%) [6, 9, 11, 43]. These findings underscore the severe medical complications associated with malnutrition in eating disorders and the critical importance of cardiovascular monitoring during inpatient treatment.

A particularly encouraging finding is the substantial reversibility of cardiovascular abnormalities with nutritional rehabilitation. Lupoglazoff et al. [6] demonstrated that electrical and echocardiographic abnormalities were fully reversible after renutrition in hospital. Wats et al. [3] reported a dramatic case of complete recovery of left ventricular dysfunction, with ejection fraction improving from 30% to 65% over 10 months of nutritional therapy. DiVasta et al. [9] documented improvement in heart rate from 48.6 to 60.3 bpm during refeeding, though 22% of patients remained bradycardic at discharge, suggesting that complete cardiovascular recovery may require longer-term weight restoration beyond initial medical stabilization.

**QTc Prolongation and Arrhythmia Risk.** QTc prolongation represents a particularly concerning finding due to its association with ventricular arrhythmias and sudden cardiac death. Giovinazzo et al.'s systematic review [27] documented ventricular arrhythmias (Torsades des Pointes, ventricular fibrillation) and sudden cardiac death as complications of AN. The relationship between QTc prolongation and electrolyte disturbances, particularly hypokalemia in binge/purging type AN, was highlighted by Ravaldi et al. [21], who identified chronic hypokalemia as a principal risk factor for death. These findings support the implementation of rigorous ECG monitoring protocols, with Proulx-Cabana et al. [43] recommending daily ECG for QTc >470 ms and continuous monitoring for QTc >500 ms.

**Structural Cardiac Changes.** Pericardial effusion, documented in 10.5-27% of severely malnourished patients [5, 6, 11, 43], represents an adaptive response to malnutrition and typically resolves with weight restoration. Toenne et al. [5] found that patients with pericardial effusion had significantly higher concentrations of creatinine, total bilirubin, and direct bilirubin, suggesting

associations with multi-organ dysfunction in severe malnutrition. Left ventricular dysfunction and reduced cardiac mass reflect the catabolic effects of starvation on cardiac muscle. Hanachi et al. [11] documented mean LV mass of 80 g (SD 22) in severely malnourished adults, substantially below normal values. The reversibility of these structural changes with nutritional rehabilitation [3, 6] demonstrates the remarkable capacity for cardiac recovery, though the time course may extend beyond initial hospitalization.

**Cardiovascular Risks During Refeeding.** The refeeding process itself carries cardiovascular risks. Giovinnazzo et al. [27] emphasized that refeeding syndrome engenders a critically increased risk of acute, life-threatening cardiac complications during the first days of refeeding. Rijn [12] noted increased cardiovascular complication risk during the first two weeks of nutritional restoration. These findings underscore the importance of gradual caloric advancement, close cardiovascular monitoring, and prophylactic electrolyte supplementation during the early refeeding period.

**Lipid Profiles and Long-Term Cardiovascular Risk.** Limited evidence examined lipid profiles and long-term cardiovascular risk. Matzkin et al. [8] found elevated total cholesterol, LDL, Apo B, and fibrinogen at admission, with decreased HDL after treatment, resulting in an undesirable lipid profile. However, the clinical significance of these findings remains unclear, as cardiovascular disease was not commonly observed in these patients. The paradoxical elevation of cholesterol in malnutrition (likely related to altered lipid metabolism and decreased cholesterol esterification) and its trajectory during refeeding warrant further investigation. Tith et al.'s study [22] of bulimia nervosa found associations with long-term cardiovascular disease risk, suggesting that eating disorders may have lasting cardiovascular consequences beyond the acute malnutrition phase.

#### **4.3 Refeeding Syndrome and Electrolyte Management**

**Incidence and Risk Factors.** The reported incidence of refeeding syndrome varied from 0-14% across studies [11, 13, 16, 43], likely reflecting differences in definitions, patient populations, monitoring intensity, and prophylactic supplementation protocols. The lower incidence rates in recent studies may reflect improved recognition and prevention strategies. Brodie et al. [13] identified lower admission weight as a significant risk factor for refeeding syndrome ( $p=0.035$ ), consistent with the understanding that severely malnourished patients face highest risk.

**Hypophosphatemia as the Hallmark of Refeeding Syndrome.** Hypophosphatemia emerged as the most clinically significant electrolyte disturbance during refeeding, with incidence ranging from 14-45% [43]. The mechanism involves insulin-stimulated cellular uptake of phosphate during carbohydrate refeeding, depleting extracellular phosphate stores. Phosphate is essential for ATP synthesis, and severe hypophosphatemia can lead to cardiac dysfunction, respiratory failure, seizures, and death. DiVasta et al. [9] documented a mean decline of 0.1 mg/dL per day in serum phosphorus during refeeding, but demonstrated that oral supplementation (250-500 mg 2-3 times daily) successfully maintained levels within the normal range. Yamazaki et al. [34] provided evidence that diets with high carbohydrate content were associated with refeeding hypophosphatemia, supporting consideration of balanced macronutrient distributions rather than carbohydrate-predominant refeeding diets.

**Multi-Electrolyte Disturbances.** Beyond phosphate, disturbances in potassium, magnesium, and other electrolytes were documented. Dunbar et al. [48] specifically examined multi-electrolyte disturbances in severely malnourished adolescents, highlighting the complexity of electrolyte management. Palma et al. [17] demonstrated significant improvement in potassium levels from admission to discharge ( $3.83 \pm 0.71$  to  $4.20 \pm 0.44$  mmol/L,  $p < 0.03$ ), reflecting successful supplementation protocols.

The association between hypokalemia and QTc prolongation, particularly in binge/purging type AN [21], emphasizes the cardiovascular implications of electrolyte disturbances.

**Prophylactic Supplementation Protocols.** A critical finding of this review is the evidence supporting prophylactic electrolyte supplementation in preventing refeeding syndrome. Gallagher et al. [41] examined prophylactic supplementation of phosphate, magnesium, and potassium for refeeding syndrome prevention. Rizzo et al. [26] found that 6 of 10 studies examining enteral nutrition provided prophylactic phosphate supplementation. Proulx-Cabana et al. [43] provided detailed supplementation protocols: phosphate 16 mmol 2-3 times daily for high-risk patients, KCl 20 mEq every 8 hours if potassium <3 mmol/L, and magnesium 250 mg three times daily if ≤0.6 mmol/L. The success of higher-calorie refeeding approaches without increased refeeding syndrome incidence [8, 11] likely reflects the concurrent implementation of prophylactic supplementation protocols.

#### 4.4 Sources of Heterogeneity

Substantial heterogeneity was observed across studies in this review, limiting the ability to conduct formal meta-analyses for most outcomes. Key sources of heterogeneity included:

- **Study Design:** The predominance of observational studies (27 of 30 studies) with only 3 RCTs limits causal inference. Retrospective designs are subject to selection bias, incomplete data capture, and confounding by indication.
- **Patient Populations:** Heterogeneity in baseline malnutrition severity (BMI 11.2-17.4 kg/m<sup>2</sup>), age groups (adolescents vs. adults), and eating disorder diagnoses (predominantly AN, with limited ARFID, BN, and atypical AN data) limits comparability.
- **MNT Interventions:** Substantial variability in initial caloric prescriptions (500-2400 kcal/day), caloric advancement rates, macronutrient composition, delivery methods, and electrolyte supplementation protocols reflects evolution of clinical practice and institutional differences.

- **Outcome Definitions:** Inconsistent definitions of weight restoration (absolute weight, kg/week, BMI, %mBMI, %IBW), refeeding syndrome (biochemical vs. clinical criteria), and medical stability complicated synthesis and comparison across studies.

- **Length of Follow-Up:** Studies varied in length of inpatient stay (11-113 days) and timing of outcome assessment, creating temporal heterogeneity that complicates comparison of outcomes.

- **Publication Era:** Studies spanning 2005-2026 capture substantial evolution in clinical practice, with earlier studies predominantly using conservative approaches while more recent studies implement higher-calorie protocols, confounding comparisons between approaches.

#### 4.5 GRADE Certainty Ratings

The certainty of evidence was assessed using GRADE methodology for key outcomes:

- **Weight Restoration (Higher-Calorie vs. Lower-Calorie Refeeding):** MODERATE certainty. Starting from high certainty based on RCT evidence [8], downgraded one level for indirectness. Supported by consistent observational evidence [2, 4, 7, 16, 20]. Conclusion: Moderate certainty that higher-calorie refeeding achieves faster weight restoration and shorter hospital stays in mildly to moderately malnourished patients.
- **Refeeding Syndrome Incidence (Higher-Calorie vs. Lower-Calorie):** MODERATE certainty. Downgraded one level for imprecision (wide confidence intervals, low event rates). Supported by systematic review evidence [11]. Conclusion: Moderate certainty that higher-calorie refeeding does not increase refeeding syndrome risk with prophylactic supplementation.
- **Cardiovascular Abnormality Reversibility:** LOW certainty. Starting from low certainty (observational evidence). Consistent direction of effect across multiple studies [3, 6, 9]. Downgraded one level for risk of bias (predominantly retrospective). Conclusion: Low certainty, though consistent reversibility demonstrated with nutritional rehabilitation.

- Hypophosphatemia Incidence During Refeeding: MODERATE certainty. Upgraded from low certainty for large magnitude of effect and dose-response relationship. Consistent findings across multiple studies [9, 34, 43]. Conclusion: Moderate certainty regarding 14-45% incidence during refeeding.

- Efficacy of Prophylactic Electrolyte Supplementation: LOW certainty. No direct RCTs due to ethical constraints. Indirect evidence from studies implementing prophylactic protocols [9, 26, 41, 43]. Conclusion: Low certainty, though clinical consensus strongly supports prophylactic supplementation.

- Severely Malnourished Patients (BMI <13 kg/m<sup>2</sup>): VERY LOW certainty. Downgraded two levels for serious imprecision and indirectness. Conclusion: Very low certainty regarding optimal refeeding approaches in severely malnourished patients.

- ARFID Weight Restoration: VERY LOW certainty. Downgraded two levels for very serious imprecision (only 2 small studies). Conclusion: Very low certainty regarding optimal MNT approaches for ARFID.

## 4.6 Clinical Implications for Inpatient MNT Protocols

Based on the synthesized evidence, several clinical implications emerge for inpatient MNT protocols:

**1. Higher-Calorie Refeeding in Mildly to Moderately Malnourished Patients.** For patients with BMI ≥13 kg/m<sup>2</sup> or %mBMI ≥65%, higher-calorie refeeding protocols starting at 1400-2000 kcal/day with daily advancement of 200-400 kcal appear safe and effective [8, 11]. This approach achieves faster weight restoration, shorter hospital stays, and reduced costs without increased refeeding syndrome risk when implemented with appropriate monitoring and prophylactic supplementation. Clinicians should consider adopting higher-calorie protocols as the standard of care for this population, moving away from overly conservative approaches.

**2. Cautious Approach for Severely Malnourished Patients.** For patients with BMI <13 kg/m<sup>2</sup> or %mBMI <65%, evidence remains insufficient to

recommend routine higher-calorie refeeding [11]. Conservative initial prescriptions (10-20 kcal/kg/day or 1000-1400 kcal/day) with gradual advancement remain appropriate. These patients require particularly intensive monitoring and may benefit from initial enteral nutrition to ensure controlled, gradual refeeding [12, 25].

**3. Prophylactic Electrolyte Supplementation.** Prophylactic supplementation protocols should be standard practice, including: phosphate supplementation for high-risk patients or when serum phosphate <2.5-3.0 mg/dL; potassium supplementation for levels <3.5 mEq/L; magnesium supplementation for levels <1.6 mEq/L; thiamine supplementation before initiating carbohydrate refeeding; and daily multivitamin supplementation.

**4. Intensive Monitoring Protocols.** Comprehensive monitoring should include: daily electrolytes (phosphate, potassium, magnesium, calcium) for first 3-7 days; daily vital signs including orthostatic changes; baseline ECG with serial monitoring for QTc prolongation; baseline echocardiography for severely malnourished patients; daily weights; fluid balance monitoring; and continuous cardiac monitoring for severe bradycardia (HR <30 bpm) or QTc >500 ms.

**5. Macronutrient Composition.** Standard macronutrient distributions (50-60% carbohydrate, 15-20% protein, 25-35% fat) appear appropriate [11]. Consideration may be given to avoiding excessively high carbohydrate content (>60%) to minimize hypophosphatemia risk [34]. The RCT by Sydney et al. [6] found no advantage to modified macronutrient composition, supporting use of standard balanced diets.

**6. Delivery Method Selection.** Meal-based oral nutrition should be the first-line approach when feasible. Enteral nutrition via nasogastric tube should be reserved for severely malnourished patients unable to meet oral intake goals, patients with persistent refusal, or medical instability requiring controlled refeeding. Combined approaches offer flexibility [19, 26].

**7. Cardiovascular Monitoring and Management.** Given the high prevalence of cardiovascular abnormalities and their reversibility: baseline

cardiovascular assessment (vital signs, ECG, echocardiography if indicated) should be standard; serial monitoring during refeeding is required to detect complications; aggressive electrolyte correction prevents arrhythmias; and clinicians should recognize that cardiovascular recovery may lag behind weight restoration, requiring continued monitoring after discharge.

**8. Multidisciplinary Approach.** Successful MNT requires coordination among physicians, dietitians, nurses, psychologists, and psychiatrists. Dietitians play a central role in meal planning, nutritional counselling, and monitoring intake [23, 53]. Psychological interventions should be integrated with nutritional rehabilitation to address underlying eating disorder psychopathology [47]. Discharge planning should include appropriate transition to outpatient or partial hospitalization programs, family involvement, and relapse prevention strategies.

## 5. Strengths and Limitations

### Strengths:

1. **Comprehensive Search Strategy:** The review employed a comprehensive search across multiple databases (PubMed, Google Scholar, SciSpace) with complementary search strategies targeting both MNT interventions and cardiovascular outcomes, identifying 279 unique papers.
2. **Rigorous Methodology:** The review followed PRISMA guidelines, employed predefined PICO criteria, conducted systematic risk of bias assessment using established tools (Cochrane RoB 2 for RCTs, adapted Newcastle-Ottawa Scale for observational studies), and applied GRADE methodology to assess certainty of evidence.
3. **Broad Scope:** The review examined multiple outcome domains (nutritional rehabilitation, cardiovascular risk, refeeding syndrome, electrolyte management) providing a comprehensive synthesis of MNT effects in eating disorders.
4. **Clinical Relevance:** The focus on inpatient populations and practical MNT protocols directly addresses clinical decision-making needs, with specific implications for protocol development.

5. **Inclusion of Recent Evidence:** The review incorporated studies published through 2026, capturing recent advances in higher-calorie refeeding approaches and contemporary clinical practice.

6. **Detailed Data Extraction:** Systematic extraction of intervention details (caloric prescriptions, macronutrient composition, delivery methods, supplementation protocols) and outcomes enables practical application of findings.

### Limitations:

1. **Predominance of Observational Evidence:** Only 3 of 30 included studies were RCTs, with the majority being retrospective or prospective observational studies. This limits causal inference and increases risk of bias from confounding, selection bias, and incomplete data capture. The certainty of evidence for most outcomes was rated as low to moderate using GRADE criteria.
2. **Substantial Heterogeneity:** Marked heterogeneity in patient populations, MNT interventions, and outcome definitions limited the ability to conduct formal meta-analyses for most outcomes. Most synthesis was qualitative rather than quantitative.
3. **Limited Evidence for Non-AN Populations:** The evidence base predominantly focused on anorexia nervosa, with very limited data for bulimia nervosa, ARFID, and atypical AN. Generalizability to these populations is uncertain.
4. **Insufficient Evidence for Severely Malnourished Patients:** Patients with BMI <13 kg/m<sup>2</sup> were underrepresented, and evidence regarding optimal refeeding approaches in this high-risk population remains insufficient for definitive recommendations.
5. **Incomplete Outcome Reporting:** Many studies did not report key outcomes of interest, particularly cardiovascular parameters (QTc interval, echocardiographic measures), lipid profiles, and long-term outcomes.
6. **Short-Term Follow-Up:** Most studies assessed outcomes only during hospitalization or at discharge, with limited data on long-term weight maintenance, cardiovascular recovery, or clinical

outcomes. The durability of inpatient weight restoration remains unclear.

7. Publication Bias: The search strategy may have missed unpublished studies or studies published in languages other than English. Positive results may be preferentially published, potentially overestimating treatment effects.

8. Geographic and Temporal Limitations: Studies were predominantly from high-income countries (United States, Australia, Europe), limiting generalizability to other settings. The temporal span (2005-2026) encompasses substantial evolution in clinical practice.

9. Lack of Standardized Definitions: Inconsistent definitions of refeeding syndrome, medical stability, and optimal weight restoration complicated synthesis and comparison across studies.

10. No Formal Protocol Registration: The protocol was not formally registered in PROSPERO or a similar registry prior to study initiation, limiting transparency regarding any post-hoc methodological decisions.

## 6. Conclusion

This systematic review synthesized evidence from 30 studies examining medical nutrition therapy in hospitalised patients with eating disorders, predominantly anorexia nervosa. The findings demonstrate that MNT effectively achieves weight restoration and medical stabilization, with important implications for optimizing inpatient refeeding protocols.

## Key Findings:

1. Higher-calorie refeeding approaches ( $\geq 1400$  kcal/day initial prescription) achieve faster weight restoration (0.76-1.98 kg/week) and shorter hospital stays (4 days reduction) compared to conservative approaches in mildly to moderately malnourished patients, without increased refeeding syndrome risk when implemented with prophylactic electrolyte supplementation and close monitoring (moderate certainty evidence).

2. Cardiovascular abnormalities are highly prevalent at admission (bradycardia 35-95%, QTc prolongation  $\sim 25\%$ , pericardial effusion 10.5-

27%, left ventricular dysfunction 15-52%) but demonstrate substantial reversibility with nutritional rehabilitation (low certainty evidence).

3. Refeeding syndrome incidence ranges from 0-14%, with hypophosphatemia occurring in 14-45% of patients. Prophylactic electrolyte supplementation protocols (phosphate, potassium, magnesium) and intensive monitoring (daily electrolytes for first 3-7 days) are essential for safe refeeding (moderate certainty for hypophosphatemia incidence; low certainty for supplementation efficacy).

4. Weight gain rate during inpatient treatment ( $\geq 0.8$  kg/week) predicts better short-term clinical outcomes, suggesting that achieving adequate weight restoration velocity is a modifiable prognostic factor.

5. Evidence for severely malnourished patients (BMI  $< 13$  kg/m<sup>2</sup>) remains insufficient to recommend routine higher-calorie refeeding, supporting continued use of cautious approaches in this high-risk population (very low certainty evidence).

6. ARFID populations may have different weight restoration trajectories compared to AN, with slower weight gain rates observed in limited studies, suggesting need for tailored approaches (very low certainty evidence).

## Clinical Implications:

For mildly to moderately malnourished patients (BMI  $\geq 13$  kg/m<sup>2</sup>), higher-calorie refeeding protocols starting at 1400-2000 kcal/day with daily advancement of 200-400 kcal should be considered standard of care, implemented with prophylactic electrolyte supplementation and intensive monitoring. For severely malnourished patients (BMI  $< 13$  kg/m<sup>2</sup>), conservative initial prescriptions (10-20 kcal/kg/day or 1000-1400 kcal/day) with gradual advancement remain appropriate. Comprehensive cardiovascular monitoring is essential given high prevalence of abnormalities and their reversibility with treatment. Macronutrient composition within recommended ranges (50-60% carbohydrate, 15-20% protein, 25-35% fat) appears appropriate,

with meal-based oral nutrition preferred when feasible.

### Research Priorities:

Future research should prioritize: (1) RCTs comparing refeeding strategies in diverse populations (severely malnourished patients, ARFID, BN, atypical AN); (2) long-term outcome studies examining weight maintenance, cardiovascular recovery, and clinical outcomes beyond hospitalization; (3) optimal macronutrient composition studies, particularly regarding carbohydrate content and hypophosphatemia risk; (4) standardized outcome definitions for refeeding syndrome, medical stability, and weight restoration targets; (5) implementation science research on barriers to adopting evidence-based refeeding protocols; (6) mechanistic studies of cardiovascular recovery and metabolic adaptation during refeeding; and (7) economic analyses and patient-centered outcomes research.

Medical nutrition therapy is effective for achieving weight restoration and medical stabilization in hospitalised patients with eating disorders. The evidence supports a paradigm shift toward higher-calorie refeeding in mildly to moderately malnourished patients, away from overly conservative approaches that prolong hospitalization without improving safety. This approach requires rigorous implementation of prophylactic electrolyte supplementation and intensive monitoring protocols. Cardiovascular abnormalities, while common and serious, demonstrate encouraging reversibility with nutritional rehabilitation. The integration of evidence-based nutritional rehabilitation with comprehensive medical monitoring and multidisciplinary psychotherapeutic interventions offers the best approach to inpatient treatment of eating disorders.

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