



Original Investigation | Nutrition, Obesity, and Exercise

# Association of Nutritional Support With Clinical Outcomes Among Medical Inpatients Who Are Malnourished or at Nutritional Risk

## An Updated Systematic Review and Meta-analysis

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### Abstract

**IMPORTANCE** Malnutrition affects a considerable proportion of the medical inpatient population. There is uncertainty regarding whether use of nutritional support during hospitalization in these patients positively alters their clinical outcomes.

**OBJECTIVE** To assess the association of nutritional support with clinical outcomes in medical inpatients who are malnourished or at nutritional risk.

**DATA SOURCES** For this updated systematic review and meta-analysis, a search of the Cochrane Library, MEDLINE, and Embase was conducted from January 1, 2015, to April 30, 2019; the included studies were published between 1982 and 2019.

**STUDY SELECTION** A prespecified Cochrane protocol was followed to identify trials comparing oral and enteral nutritional support interventions with usual care and the association of these treatments with clinical outcomes in non-critically ill medical inpatients who were malnourished.

**DATA EXTRACTION AND SYNTHESIS** Two reviewers independently extracted data and assessed risk of bias; data were pooled using a random-effects model.

**MAIN OUTCOMES AND MEASURES** The primary outcome was mortality. The secondary outcomes included nonelective hospital readmissions, length of hospital stay, infections, functional outcome, daily caloric and protein intake, and weight change.

**RESULTS** A total of 27 trials (n = 6803 patients) were included, of which 5 (n = 3067 patients) were published between 2015 and 2019. Patients receiving nutritional support compared with patients in the control group had significantly lower rates of mortality (230 of 2758 [8.3%] vs 307 of 2787 [11.0%]; odds ratio [OR], 0.73; 95% CI, 0.56-0.97). A sensitivity analysis suggested a more pronounced reduction in the risk of mortality in recent trials (2015 or later) (OR, 0.47; 95% CI, 0.28-0.79) compared with that in older studies (OR, 0.94; 95% CI, 0.72-1.22), in patients with established malnutrition (OR, 0.52; 95% CI, 0.34-0.80) compared with that in patients at nutritional risk (OR, 0.85; 95% CI, 0.62-1.18), and in trials with high protocol adherence (OR, 0.67; 95% CI, 0.54-0.84) compared with that in trials with low protocol adherence (OR, 0.88; 95% CI, 0.44-1.76). Nutritional support was also associated with a reduction in nonelective hospital readmissions (14.7% vs 18.0%; risk ratio, 0.76; 95% CI, 0.60-0.96), higher energy intake (mean difference, 365 kcal; 95% CI, 272-458 kcal) and protein intake (mean difference, 17.7 g; 95% CI, 12.1-23.3 g), and weight increase

(continued)

### Key Points

**Question** What is the association of nutritional support with clinical outcomes in medical inpatients who are malnourished or at nutritional risk?

**Findings** In this updated systematic review and meta-analysis of 27 trials including 6803 patients, nutritional support provided during hospitalization was associated with significantly lower rates of mortality and nonelective hospital readmissions, as well as higher energy and protein intake and weight increase.

**Meaning** This study's findings suggest that nutritional support in hospitalized patients who are malnourished or at nutritional risk is associated with improved nutritional and clinical outcomes and should be considered when treating this population.

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Abstract (continued)

(0.73 kg; 95% CI, 0.32-1.13 kg). No significant differences were observed in rates of infections (OR, 0.86; 95% CI, 0.64-1.16), functional outcome (mean difference, 0.32; 95% CI, -0.51 to 1.15), and length of hospital stay (mean difference, -0.24; 95% CI, -0.58 to 0.09).

**CONCLUSIONS AND RELEVANCE** This study's findings suggest that despite heterogeneity and varying methodological quality among trials, nutritional support was associated with improved survival and nonelective hospital readmission rates among medical inpatients who were malnourished and should therefore be considered when treating this population.

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## Introduction

Malnutrition is a major public health problem, particularly in the multimorbid medical population, affecting more than 30% of hospitalized patients.<sup>1-4</sup> It results from the complex interplay of different predisposing factors, including immobilization and advanced age and the associations of illness with protein and energy homeostasis, protein catabolism, hormonal function, and appetite that lead to progressive weight loss and sarcopenia.<sup>5,6</sup>

Malnutrition is a major risk factor associated with high mortality and morbidity, functional decline, prolonged hospital stays, and increased health care costs.<sup>2,7</sup> Nutritional support, when provided during the hospital stay, may offset some of these adverse outcomes. For this reason, international societies<sup>4,8</sup> recommend screening patients for malnutrition risk and using nutritional support in patients at nutritional risk or who are malnourished. However, these recommendations have been largely based on physiological rationales. Two meta-analyses of trials investigating the use of nutritional support for medical and mixed medical, surgical, and critically ill inpatients did not find significant associations with outcomes, including mortality and several complications.<sup>9,10</sup> Yet, the quality of the included studies was low, limiting any strong conclusions.

Considering these results, some authors have argued against the routine use of nutritional support in treating medical inpatients at nutritional risk and classified nutritional interventions as "services for which harms are likely to outweigh benefits."<sup>11</sup> Since the publication of the previously mentioned meta-analyses,<sup>9,10</sup> however, several large, high-quality trials were published that may change the overall conclusions. Therefore, our aim was to perform an updated systematic review and meta-analysis to assess the associations of nutritional support with clinical outcomes in non-critically ill medical inpatients with malnutrition or at nutritional risk, overall and stratified by different subgroups.

## Methods

The methods used for this updated systematic review and meta-analysis were consistent with an initial analysis,<sup>9</sup> which followed a prespecified Cochrane protocol<sup>12</sup> and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines,<sup>13</sup> as summarized below.

## Data Sources and Searches

The literature searches were conducted in the Cochrane Library, MEDLINE, and Embase electronic databases from January 1, 2015, just after the last date reviewed in the prior meta-analysis,<sup>9</sup> to April 30, 2019. An example of the search strategy used in MEDLINE is provided in the eAppendix in the [Supplement](#). In addition, we searched bibliographies of review articles and the ClinicalTrials.gov registry for ongoing or unpublished trials. Authors of ongoing nutritional support studies were also contacted. There were no language restrictions.

## Study Selection

We systematically searched the literature to identify randomized and nonrandomized clinical trials (RCTs) that allocated non-critically ill medical inpatients who are malnourished or at nutritional risk (based on body mass index, the presence of a disease associated with malnutrition, or the use of a nutritional assessment or screening tool) to a nutritional support intervention or a control group. Medical inpatients were defined as patients hospitalized in medical wards of acute care institutions (including those of geriatrics, gastroenterology, cardiology, pulmonology, general internal medicine, infectious diseases, nephrology, and oncology). The exclusion criteria were as follows: studies conducted in outpatient care settings, nursing homes, long-term care facilities, or intensive care units and trials focusing on surgical patients, patients with pancreatitis (because of their particular nutritional needs and the management of this condition), and those receiving palliative care.

We included studies with interventions consisting of any type of nutritional support (including dietary advice, changes in the organization of nutritional care, food fortification, extra snacks, oral nutrition supplements, and enteral tube feeding) except parenteral nutrition, independent of the duration of the intervention.

The primary study outcome was all-cause mortality, defined as death from any cause and measured at hospital discharge or at follow-up (up to 6 months after randomization). Secondary end points included nosocomial infections, nonelective readmissions, functional outcome (assessed by the Barthel index score at follow-up), length of hospital stay (LOS), daily energy and protein intake, and body weight change. We also gathered information about adherence to the nutritional intervention and the study protocol. Older studies were defined as those published before 2015<sup>14-33</sup> (included in the original meta-analysis<sup>9</sup>) and newer studies as those published since 2015<sup>34-38</sup> (identified in the updated meta-analysis).

## Data Extraction and Quality Assessment

Two of us (F.G. and A.B.) independently screened abstracts, extracted relevant data from the studies that met the inclusion criteria, and assessed their risk of bias. Disagreements were resolved by consulting one of us (P.S.). Two of us (A.B. and L.B.) assessed the trials in which another 2 of us (N.E.D. and P.S.) were directly involved.<sup>36,38</sup> As recommended by the Cochrane Collaboration, the following criteria were used to assess risk of bias: random sequence generation (selection bias); randomization concealment (selection bias); blinding (performance bias and detection bias), separated for blinding of participants and personnel, and blinding of outcome assessment; incomplete outcome data (attrition bias); selective reporting (reporting bias); and other bias.

## Statistical Analysis

Dichotomous data were reported as odds ratios (ORs) or risk ratios (RRs) with 95% CIs and continuous data as the mean differences with 95% CIs. Data were pooled using a random-effects model.

We identified heterogeneity through visual inspection of the forest plots and also considered the  $I^2$  statistic, which quantifies inconsistency across studies. An  $I^2$  statistic value of 50% or more indicates a considerable level of heterogeneity. We used visual inspection of funnel plots to assess publication bias.

We conducted the following subgroup analyses: stratification by degree of malnutrition (established malnutrition vs risk of malnutrition), by baseline mortality rate in the control group (high mortality [ $\geq 10\%$ ] vs low mortality [ $< 10\%$ ]), by adherence to the nutrition protocol (high adherence vs low adherence, as described in the eTable in the [Supplement](#)), by route of nutritional support (oral vs mixed routes), and by publication year (older [2014 or earlier] vs newer [2015 or later]).

All of the analyses were conducted with statistical significance set at  $P = .05$ , and the testing was 2-sided. Most figures were produced using Review Manager, version 5.3 (Cochrane Collaboration).

## Results

After discarding duplicates, we identified 265 abstracts from the 3 electronic databases and 5 additional records through manual searches and contact with experts. Five new eligible trials including 3067 participants that were published between 2015 and 2019 were identified. Among these 5 trials were 2 large trials including 652 patients<sup>36</sup> and 2028 patients.<sup>38</sup> Data from these 5 trials were extracted and added to the original data file.<sup>9</sup> The final analysis included a total of 27 trials with 6803 patients (including 5 from the new search and 22 from the previous one) (eFigure 1 in the Supplement). **Table 1** provides an overview of the characteristics of these included studies.

Assessment of risk of bias, which was performed as recommended by the Cochrane Collaboration (risk of bias graph in eFigure 2 in the Supplement), revealed that of the 27 studies, 17 had a low risk of random sequence generation and randomization concealment bias, 15 had a low risk of attrition bias for objective outcomes, and 19 had a low risk of reporting bias. Approximately 70% of the studies had high risk of performance bias for objective outcomes because blinding of participants and personnel was not undertaken. There was a large proportion of unclear risk of bias related to studies not reporting subjective outcomes. Other biases were not detected in most trials. Overall, risk of bias was less pronounced in the present study compared with the initial report,<sup>9</sup> with newer trials showing better methodological quality. Funnel plots revealed no evidence of publication bias.

### Primary Outcome

The analyses of the outcomes in the overall population and in subgroups are provided in **Table 2**. A total of 17 studies<sup>14-16,18-20,23,24,26,30,32,34-36,38,40,41</sup> (13 older and 4 newer) reported data on mortality, the primary outcome. The association of the intervention with mortality risk for each trial, as well as the overall association stratified by newer vs older trials is shown in **Figure 1**. The mortality rate was 8.3% (230 of 2758) among the intervention group patients compared with 11.0% (307 of 2787) among the control group patients (OR, 0.73; 95% CI, 0.56-0.97,  $P = .03$ ). There was a low level of heterogeneity among trials ( $I^2 = 35%$ ,  $P = .08$ ) (Table 2). This significant reduction in mortality associated with the nutritional support was different from the nonsignificant association observed in the original meta-analysis (OR, 0.96; 95% CI, 0.72-1.27).<sup>9</sup>

### Secondary Outcomes

Rates of nonelective hospital readmissions were reported in 9 studies<sup>16,17,20,31,34,36,38-40</sup> (Table 2 and **Figure 2**). Compared with the control group, nutritional support interventions were associated with a significant reduction of nonelective hospital readmissions (14.7% [280 of 1903] in the intervention vs 18.0% [339 of 1880] in the control group; RR, 0.76; 95% CI, 0.60-0.96;  $P = .02$ ), although there was heterogeneity among trials ( $I^2 = 48%$ ,  $P = .05$ ). There was no statistically significant difference between the older and newer studies. The original meta-analysis<sup>9</sup> had also reported an association between nutritional support and reduced nonelective hospital readmissions (RR, 0.71; 95% CI, 0.57-0.87).

Compared with the control group, the intervention group patients had no differences in rates for infections (4.8% [88 of 1817] vs 5.6% [102 of 1825]; OR, 0.86; 95% CI, 0.64-1.16), functional outcome at follow-up (17.3 vs 16.9 points; mean difference in Barthel index score, 0.32 points; 95% CI, -0.51 to 1.15), or LOS (11.5 days vs 12.0 days; mean difference, -0.24 days; 95% CI, -0.58 to 0.09) (Table 2 and eFigures 3, 4, and 5 in the Supplement).

Regarding nutritional outcomes (Table 2 and eFigures 6, 7, and 8 in the Supplement), nutritional support interventions were associated with a significantly higher energy intake (1618 kcal in the intervention group vs 1331 kcal in the control group; mean difference, 365 kcal; 95% CI, 272-458 kcal) and protein intake (59 g in the intervention group vs 48 g in the control group; mean difference, 17.7 g; 95% CI, 12.1-23.3 g). In addition, there was a significant increase in body weight (0.63 kg in the intervention group vs -0.19 kg in the control group; mean difference, 0.73 kg; 95% CI, 0.32-1.13 kg).

Table 1. Overview of Included Studies

| Source                                       | Patient Population                                       | Country         | Total Sample Size | Intervention Group   | Control Group  |
|--|--|-----------------|-------------------|--|--|
| Bonilla-Palomas et al, <sup>34</sup> 2016    | Acute decompensated heart failure                        | Spain           | 120               | Conventional treatment for heart failure combined with an individualized nutritional intervention: diet optimization, specific recommendations, ONS if nutritional goals were not reached, for 6 mo  | Conventional treatment for heart failure   |
| Broqvist et al, <sup>14</sup> 1994           | Acute decompensated heart failure                        | Sweden          | 21                | Normal hospital food and between meals with 500 mL ONS daily containing 30 g protein and 750 kcal  | Normal hospital food and 1:10 diluted placebo version of ONS   |
| Bunout et al, <sup>15</sup> 1989             | Alcoholic liver disease                                  | Chile           | 36                | Oral diet including 50 kcal/kg/d, 1.5 g protein/kg/d, casein-based product   | Standard diet  |
| Cano-Torres et al, <sup>35</sup> 2017        | General medical inpatients                               | Mexico          | 55                | Individualized nutrition plan according to energy and protein (1.0-1.5 g/kg) intake requirements as well as dietary advice based on face-to-face interviews with patients and their caregivers or family members, until hospital discharge   | Standard nutritional management  |
| Deutz et al, <sup>36</sup> 2016              | General medical inpatients (≥65 y of age)                | United States   | 652               | 2 Bottles ONS daily providing 700 kcal/d, 40 g protein/d, 3 g calcium-beta-hydroxybeta-methylbutyrate, 160 IU vitamin D, and other essential micronutrients, for 90 d  | 2 Bottles placebo ONS providing 96 kcal and 20 mg vitamin C  |
| Feldblum et al, <sup>33</sup> 2011           | General medical inpatients (≥65 y of age)                | Israel          | 259               | Individual nutritional treatment, 237 mL containing 12.6 g fat, 13 g protein, and 47.3 g carbohydrates (total, 360 kcal), additional food fortification  | Routine care on request  |
| Gariballa et al, <sup>16</sup> 2006          | General medical inpatients (≥65 y of age)                | United Kingdom  | 445               | 2 Bottles (200 mL each) ONS daily, 995 kcal/d plus vitamins  | Oral placebo (60 kcal)   |
| Gazzotti et al, <sup>17</sup> 2003           | General medical inpatients (≥75 y of age)                | Belgium         | 80                | Standard hospital food and 1 Clinutren soup, 500 kcal/d, 21 g protein/d  | Standard hospital food, no supplements   |
| Hickson et al, <sup>18</sup> 2004            | General medical inpatients (≥65 y of age)                | United Kingdom  | 592               | Nutritional care from health care assistants, snacks and drinks  | Usual care   |
| Hogarth et al, <sup>19</sup> 1996            | General geriatric inpatients                             | United Kingdom  | 25                | Intervention 1: daily 750 mL oral glucose supplement (540 kcal) and capsules containing vitamins A (8000 U), B <sub>1</sub> (15 mg), B <sub>2</sub> (15 mg), B <sub>3</sub> (50 mg), B <sub>6</sub> (10 mg), and C (500 mg), for 1 mo<br>Intervention 2: daily 750 mL oral glucose supplement (540 kcal) and placebo capsules for 1 mo | Control 1: Nutrasweet glucose drink and capsules containing vitamins A (8000 U), B <sub>1</sub> (15 mg), B <sub>2</sub> (15 mg), B <sub>3</sub> (50 mg), B <sub>6</sub> (10 mg), and C (500 mg), for 1 mo<br>Control 2: Nutrasweet glucose drink and placebo capsules for 1 mo |
| Holyday et al, <sup>20</sup> 2012            | General geriatric inpatients                             | Australia       | 143               | Individual modification of hospital meals (fortification), nutrition supplements   | Individual modification only on request  |
| Huynh et al, <sup>37</sup> 2015              | General medical inpatients                               | India           | 212               | Dietary counseling +2 bottles ONS daily providing 432 kcal/d and 16 g protein/d plus micronutrients, for 12 weeks  | Dietary counseling alone   |
| McEvoy and James, <sup>21</sup> 1982         | General medical inpatients                               | United Kingdom  | 54                | 2 Sachets oral "Build-Up" daily, 36.4 g protein and 644 kcal   | Normal hospital diet   |
| McWhirter and Pennington, <sup>22</sup> 1996 | General medical inpatients                               | United Kingdom  | 86                | (a) ONS containing 566 kcal/d, 23.9 g protein/d<br>(b) Nocturnal tube feeding (nasogastric tube), additional intake of 84 kcal/d and 29.5 g protein/d  | Standard hospital diet   |
| Munk et al, <sup>23</sup> 2014               | Inpatients from oncology, orthopedics, and urology wards | Denmark         | 81                | Protein-enriched small dishes supplementary to standard food service, ONS or snacks  | Standard hospital diet   |
| Neelemaat et al, <sup>24</sup> 2012          | General medical inpatients (≥60 y of age)                | The Netherlands | 210               | Energy- and protein-enriched diet, 2 additional servings of ONS, 2520 kJ/d (to convert to kcal, divide by 4.186), 24 g protein/d, orally 400 U Vitamin D <sub>3</sub> and 500 mg calcium/d, telephone counseling   | Usual care   |

(continued)

Table 1. Overview of Included Studies (continued)

| Source   | Patient Population                                  | Country         | Total Sample Size | Intervention Group   | Control Group   |
|--|---|-----------------|-------------------|--|---|
| Ollenschläger et al, <sup>25</sup> 1992                                | Patients with induction treatment for leukemia      | Germany         | 29                | Menus of free choice, nutritional education, daily visits by the dietician, and record of food intake  | Menus of free choice, no nutritional education  |
| Potter et al, <sup>26</sup> 2001 and Roberts et al, <sup>27</sup> 2003 | General geriatric inpatients                        | United Kingdom  | 381               | 120 mL oral sip-feed supplement 3/d, 540 kcal/d, 22.5 g protein  | Normal hospital food  |
| Rüfenacht et al, <sup>28</sup> 2010                                    | General medical inpatients                          | Switzerland     | 36                | Individual nutritional plan with food enrichment, energy- and/or protein-rich snacks, beverages and energy-dense ONS   | 2 U ONS providing 200 mL each with 300 kcal and 12 g protein                                  |
| Ryan et al, <sup>29</sup> 2004   | General medical inpatients (≥65 y of age)           | France          | 16                | Oral supplement (1050 kJ [to convert to kcal, divide by 4.186], 250 mL)  | Standard hospital breakfast   |
| Saudny-Unterberger et al, <sup>30</sup> 1997                           | Inpatients with COPD exacerbation (40-85 y of age)  | Canada          | 33                | ONS, 39 kcal/kg/d  | Standard food, 29 kcal/kg/d   |
| Schuetz et al, <sup>38</sup> 2019                                      | General medical inpatients                          | Switzerland     | 2028              | A systematic nutritional assessment by a dietician was done to define nutritional targets, followed by individualized early nutritional support based on a previously published consensus algorithm and current nutritional guidelines | Standard nutritional management   |
| Somanchi et al, <sup>39</sup> 2011                                     | General medical inpatients                          | United States   | 400               | Nutritional screening of all patients, clinical nutritional plan initiated by the nurse manager  | Usual hospital screening and nutritional counseling on demand                                 |
| Starke et al, <sup>40</sup> 2011                                       | General medical inpatients                          | Switzerland     | 132               | Individual nutritional care (food supply, fortification of meals with maltodextrins, rapeseed oil, cream and/or protein, powder, in-between snacks, and ONS); protein intake 1.0 g/kg body weight                                      | Standard nutritional care, including prescription of ONS upon discretion of physician         |
| Vermeeren et al, <sup>31</sup> 2004                                    | Inpatients with COPD exacerbation                   | The Netherlands | 56                | Liquid oral supplement 3x 125 mL, 2.38 MJ/d (to convert to kcal, divide by 0.0041858), 20 energy % protein, 20 energy % fat, and 60 energy % carbohydrate, standardized dietetic consultation  | Free choice of normal hospital food and placebo 3 × 125 mL, 0 MJ/d                            |
| Vlaming et al, <sup>32</sup> 2001                                      | General medical, surgical, or orthopedic inpatients | United Kingdom  | 549               | Normal hospital food plus 400 mL oral sip-feed supplement, 600 kcal/d, 25.0 g protein/d, 80.8 g carbohydrates/d, 19.6 g fat/d, multivitamins   | Normal hospital food plus 400 mL placebo, 100 kcal/d, 25 g carbohydrates/d plus multivitamins |
| Volkert et al, <sup>41</sup> 1996                                      | General geriatric inpatients                        | Germany         | 72                | Normal hospital food and 400 mL/d (2100 kJ [to convert to kcal divide by 4.186]) liquid supplement, 200 mL/d (1050 kJ) for the following 6 mo at home  | Normal hospital food, usual care without supplements  |

Abbreviations: COPD, chronic obstructive pulmonary disease; ONS, oral nutrition supplements.

Heterogeneity among trials was high ( $I^2 = 84%$  [energy intake],  $I^2 = 88%$  [protein intake], and  $I^2 = 100%$  [weight change]).

### Sensitivity Analyses

Trials were stratified according to the degree of malnutrition, baseline mortality rate in the control group, adherence to the nutrition protocol, route of nutritional support, and publication year (before or after 2015) (Table 2).

The sensitivity analysis suggested a more pronounced reduction in the risk of mortality in recent trials (2015 or later) (OR, 0.47; 95% CI, 0.28-0.79) compared with that in older studies (OR, 0.94; 95% CI, 0.72-1.22), in patients with established malnutrition (OR, 0.52; 95% CI, 0.34-0.80) compared with that in patients at nutritional risk (OR, 0.85; 95% CI, 0.62-1.18), and in trials with high protocol adherence (OR, 0.67; 95% CI, 0.54-0.84) compared with that in trials with low protocol adherence (OR, 0.88; 95% CI, 0.44-1.76).

The results suggest larger benefits associated with nutritional support for the subgroup of patients with established malnutrition compared with that for the subgroup of patients at nutritional risk, particularly for functional outcome and nonelective hospital readmissions (and a beneficial

association between nutritional support and mortality and LOS). Among the individuals with a higher mortality rate ( $\geq 10\%$ ) vs those with a lower mortality rate ( $< 10\%$ ), the associations of the intervention were stronger. However, this effect was only significant for nonelective readmissions and energy intake.

There was no evidence of other associations in subgroup analyses based on protocol adherence or route of nutritional support except for energy intake and weight change, which was increased in the studies with high adherence to the nutrition protocol (energy intake [402 kcal]; weight change [0.87 kg]) compared with the studies with lower adherence (energy intake [107 kcal]; weight change [-0.20 kg]). Associations between nutritional support and mortality reduction and weight gain were more pronounced in newer studies compared with the older trials.

**Table 2. Outcome Analyses: Overall Population and Subgroups**

| Population/Variable  | Mortality, OR (95% CI) | Infections, OR (95% CI) | Nonelective Readmissions, Risk Ratio (95% CI) | Mean Difference (95% CI)        |                        |                           |                         |                        |
|--|------------------------|-------------------------|---|---------------------------------|------------------------|---------------------------|-------------------------|------------------------|
|  |                        |                         |   | Function, Barthel Index, Points | Length of Stay, d      | Daily Energy Intake, kcal | Daily Protein Intake, g | Weight Change, kg      |
| <b>Overall population</b>  |                        |                         |   |                                 |                        |                           |                         |                        |
| Intervention, events/total (%) or mean, No.                            | 230/2758 (8.3)         | 88/1817 (4.8)           | 280/1903 (14.7)                               | 17.3                            | 11.5                   | 1618                      | 59                      | 0.63                   |
| Control, events/total (%) or mean, No.                                 | 307/2787 (11.0)        | 102/1825 (5.6)          | 339/1880 (18.0)                               | 16.9                            | 12.0                   | 1331                      | 48                      | -0.19                  |
| Overall OR mean difference (95% CI)                                    | 0.73 (0.56 to 0.97)    | 0.86 (0.64 to 1.16)     | 0.76 (0.60 to 0.96)                           | 0.32 (-0.51 to 1.15)            | -0.24 (-0.58 to 0.09)  | 365 (272 to 458)          | 17.7 (12.1 to 23.3)     | 0.73 (0.32 to 1.13)    |
| I <sup>2</sup> Test for overall effect, %                              | 35                     | 0                       | 48  | 77                              | 0                      | 84                        | 88                      | 100                    |
| <b>Subgroup analysis stratified by degree of malnutrition</b>          |                        |                         |   |                                 |                        |                           |                         |                        |
| Established malnutrition   | 0.52 (0.34 to 0.80)    | NA                      | 0.36 (0.20 to 0.64)                           | 4.00 (1.69 to 6.31)             | -2.08 (-4.19 to 0.02)  | 304 (218 to 389)          | 16.1 (5.1 to 27.1)      | 0.96 (0.42 to 1.50)    |
| At nutritional risk  | 0.85 (0.62 to 1.18)    | 0.86 (0.64 to 1.15)     | 0.86 (0.74 to 1.00)                           | 0.02 (-0.54 to 0.59)            | -0.17 (-0.51 to 0.17)  | 394 (262 to 526)          | 16.3 (9.8 to 22.9)      | 0.86 (0.79 to 0.93)    |
| I <sup>2</sup> Test for subgroup difference, %                         | 69                     | NA                      | 88  | 91                              | 68                     | 21                        | 0                       | 0                      |
| <b>Subgroup analysis stratified by mortality rate in control group</b> |                        |                         |   |                                 |                        |                           |                         |                        |
| High mortality ( $\geq 10\%$ )   | 0.61 (0.43 to 0.87)    | 0.77 (0.17 to 3.46)     | 0.28 (0.12 to 0.65)                           | 0.85 (-1.47 to 3.16)            | -1.32 (-2.52 to -0.12) | 231 (81 to 280)           | 16.0 (2.9 to 29.2)      | 0.14 (-0.61 to 0.88)   |
| Low mortality ( $< 10\%$ )   | 0.91 (0.59 to 1.40)    | 0.86 (0.64 to 1.17)     | 0.86 (0.72 to 1.02)                           | 0.14 (-0.70 to 0.98)            | -0.12 (-0.49 to 0.24)  | 428 (316 to 540)          | 16.8 (9.9 to 23.6)      | 0.86 (0.79 to 0.93)    |
| I <sup>2</sup> Test for subgroup difference, %                         | 49                     | 0                       | 85  | 0                               | 71                     | 77                        | 0                       | 73                     |
| <b>Stratification by adherence to nutrition protocol</b>               |                        |                         |   |                                 |                        |                           |                         |                        |
| High adherence   | 0.67 (0.54 to 0.84)    | 0.89 (0.62 to 1.26)     | 0.91 (0.76 to 1.10)                           | 0.56 (0.07 to 1.05)             | -0.17 (-0.52 to 0.19)  | 402 (313 to 491)          | 19.6 (12.9 to 26.3)     | 0.87 (0.81 to 0.93)    |
| Low adherence  | 0.88 (0.44 to 1.76)    | 0.79 (0.45 to 1.38)     | 0.58 (0.36 to 0.96)                           | 0.33 (-0.88 to 1.55)            | -0.82 (-1.80 to 0.16)  | 107 (24 to 191)           | 8.3 (-3.2 to 19.8)      | -0.20 (-0.23 to -0.17) |
| I <sup>2</sup> Test for subgroup difference, %                         | 0                      | 0                       | 64  | 0                               | 34                     | 96                        | 64                      | 100                    |
| <b>Stratification by route of nutritional support</b>                  |                        |                         |   |                                 |                        |                           |                         |                        |
| Oral routes  | 0.74 (0.58 to 0.93)    | 0.75 (0.50 to 1.11)     | 0.74 (0.56 to 0.99)                           | 0.33 (-0.88 to 1.55)            | -0.26 (-0.67 to 0.15)  | 367 (247 to 487)          | 16.2 (9.5 to 22.8)      | 0.761 (0.27 to 1.14)   |
| Mixed routes   | 0.71 (0.52 to 0.97)    | 1.02 (0.65 to 1.61)     | 0.73 (0.35 to 1.53)                           | 0.56 (0.07 to 1.05)             | -0.98 (-3.32 to 1.36)  | 417 (108 to 727)          | 28.8 (-9.0 to 66.6)     | 0.90 (0.89 to 0.91)    |
| I <sup>2</sup> Test for subgroup difference, %                         | 0                      | 6                       | 0   | 0                               | 0                      | 0                         | 0                       | 0                      |
| <b>Stratification by publication year</b>                              |                        |                         |   |                                 |                        |                           |                         |                        |
| Older (2014 or earlier)  | 0.94 (0.72 to 1.22)    | 0.75 (0.50 to 1.11)     | 0.71 (0.57 to 0.87)                           | 0.33 (-0.88 to 1.55)            | -0.42 (-1.09 to 0.24)  | 396 (272 to 520)          | 18.5 (11.2 to 25.9)     | 0.66 (0.17 to 1.15)    |
| Newer (2015 or later)  | 0.47 (0.28 to 0.79)    | 1.02 (0.65 to 1.61)     | 0.78 (0.50 to 1.22)                           | 0.56 (0.07 to 1.05)             | -0.27 (-0.87 to 0.33)  | 286 (239 to 333)          | 10.0 (8.1 to 11.9)      | 0.86 (0.78 to 0.95)    |
| I <sup>2</sup> Test for subgroup difference, %                         | 81                     | 6                       | 0   | 0                               | 0                      | 62                        | 79                      | 0                      |

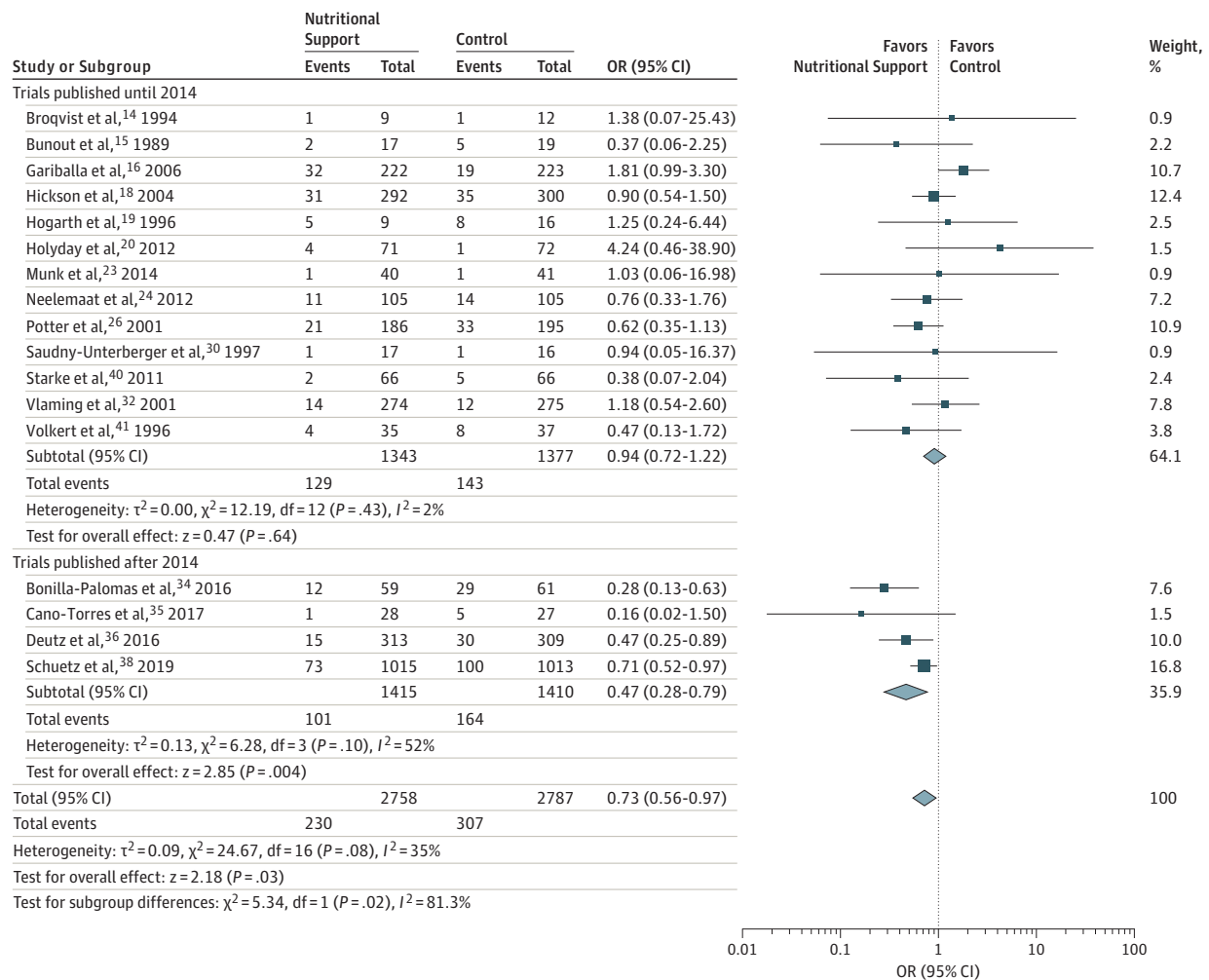
Abbreviations: NA, not applicable; OR, odds ratio.

An additional sensitivity analysis was performed to better understand whether associations of nutritional support would be similar if the largest trial (EFFORT [Effect of Early Nutritional Support on Frailty, Functional Outcomes, and Recovery of Malnourished Medical Inpatients Trial]<sup>38</sup>) was excluded (Table 3). When excluding EFFORT trial data from the analysis, associations of nutritional support with mortality (OR, 0.73; 95% CI, 0.52-1.03), as well as nonelective hospital readmissions (RR, 0.71; 95% CI, 0.54-0.94), were similar.

## Discussion

The findings of this updated systematic review and meta-analysis of RCTs investigating the association of nutritional support interventions with outcomes in medical inpatients who are malnourished or at nutritional risk were 3-fold. First, compared with the original meta-analysis<sup>9</sup> that included trials published before April 2014 (9 trials), the 5 new trials were a higher quality, had lower bias, and collectively nearly doubled the total patient population studied in this updated meta-analysis (3736 patients from the original study plus 3067 patients from the 5 new studies). Newer trials also differed with regard to the nutritional interventions used, with a higher quality of protein<sup>13</sup>

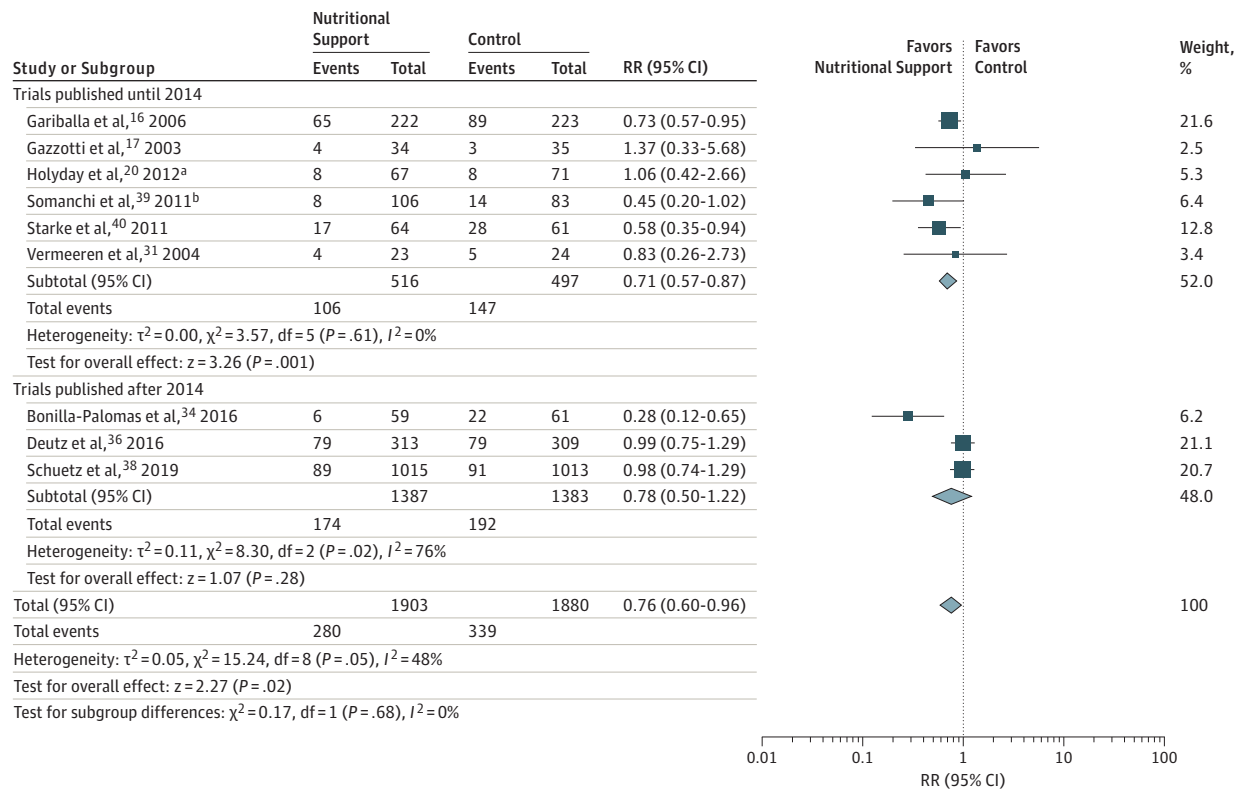
Figure 1. Forest Plot Comparing Nutritional Intervention vs Control for Mortality, Stratified by Publication Year



A Mantel-Haenszel random-effects model was used. Squares indicate mean values, with the size of squares reflecting the weight and the lines indicating 95% CIs. Diamonds indicate pooled estimates, with horizontal points of the diamonds indicating 95% CIs. OR indicates odds ratio.



Figure 2. Forest Plot Comparing Nutritional Intervention vs Control for Nonelective Hospital Readmissions, Stratified by Publication Year



A Mantel-Haenszel random-effects model was used. Squares indicate mean values, with the size of squares reflecting the weight and the lines indicating 95% CIs. Diamonds indicate pooled estimates, with horizontal points of the diamonds indicating 95% CIs. RR indicates risk ratio.

<sup>a</sup> Calculated and approximated from readmission frequency.

<sup>b</sup> Calculated and approximated from readmission rate.

Table 3. Outcome Analyses With and Without EFFORT<sup>38</sup>

| Population/Variable                         | Mortality, OR (95% CI) | Infections, OR (95% CI) | Nonelective Readmissions, Risk Ratio (95% CI) | Mean Difference (95% CI)        |                       |                           |                         |                     |
|---|------------------------|-------------------------|---|---------------------------------|-----------------------|---------------------------|-------------------------|---------------------|
|   |                        |                         |   | Function, Barthel Index, Points | Length of Stay, d     | Daily Energy Intake, kcal | Daily Protein Intake, g | Weight Change, kg   |
| Overall population                          |                        |                         |   |                                 |                       |                           |                         |                     |
| Intervention, events/total (%) or mean, No. | 230/2758 (8.3)         | 88/1817 (4.8)           | 280/1903 (14.7)                               | 17.3                            | 11.5                  | 1618                      | 59                      | 0.63                |
| Control, events/total (%) or mean, No.      | 307/2787 (11.0)        | 102/1825 (5.6)          | 339/1880 (18.0)                               | 16.9                            | 12.0                  | 1331                      | 48                      | -0.19               |
| Overall estimate                            | 0.73 (0.56 to 0.97)    | 0.86 (0.64 to 1.16)     | 0.76 (0.60 to 0.96)                           | 0.32 (-0.51 to 1.15)            | -0.24 (-0.58 to 0.09) | 365 (272 to 458)          | 17.7 (12.1 to 23.3)     | 0.73 (0.32 to 1.13) |
| $I^2$ Test for overall effect, %            | 35                     | 0                       | 48  | 77                              | 0                     | 84                        | 88                      | 100                 |
| Overall population without EFFORT           |                        |                         |   |                                 |                       |                           |                         |                     |
| Intervention, events/total (%) or mean, No. | 157/1743 (9.0)         | 48/802 (5.9)            | 191/888 (21.5)                                | 15.5                            | 12.8                  | 1950                      | 73                      | 0.37                |
| Control, events/total (%) or mean, No.      | 207/1774 (11.7)        | 63/812 (7.8)            | 248/867 (28.6)                                | 14.8                            | 14.0                  | 1543                      | 54                      | -0.21               |
| Overall estimate                            | 0.73 (0.52 to 1.03)    | 0.75 (0.50 to 1.11)     | 0.71 (0.54 to 0.94)                           | 0.33 (-0.88 to 1.55)            | -0.38 (-0.85 to 0.10) | 382 (266 to 498)          | 18.5 (11.2 to 26.9)     | 0.71 (0.27 to 1.14) |
| $I^2$ Test for overall effect, %            | 39                     | 0                       | 47  | 78                              | 5                     | 84                        | 89                      | 99                  |

Abbreviations: EFFORT, Effect of Early Nutritional Support on Frailty, Functional Outcomes, and Recovery of Malnourished Medical Inpatients Trial; OR, odds ratio.

and a more individualized, patient-specific approach. Second, our analysis suggests that nutritional support compared with no support was statistically significantly associated with increased protein and energy intake during the hospital stay, with an increased body weight. Third, our analysis found that nutritional support was associated with a statistically significant reduction in mortality and nonelective hospital readmissions and thus had favorable associations with clinical outcomes beyond the known associations with metabolic parameters.

There are important differences in the results between the original meta-analysis<sup>9</sup> and the present updated analysis, particularly with regard to mortality. In the original analysis, the mortality difference was 0.5% in favor of nutritional support,<sup>9</sup> whereas the absolute mortality benefit increased to 2.8% in the present updated analysis, corresponding to a number needed to treat of 36 to prevent 1 death. The inclusion of 2 recent, large, and high-quality RCTs—namely EFFORT<sup>38</sup> and NOURISH (Nutrition Effect on Unplanned Readmissions and Survival in Hospitalized Patients)<sup>36</sup> that reported lower mortality associated with nutritional support—may have contributed to this shift in results, although overall heterogeneity regarding the mortality outcome was only low to moderate. This finding suggests that the decreased risk of mortality may have been masked in older studies owing to small sample sizes (eg, 22 patients<sup>14</sup>), lower study quality, and quality of nutritional support used in trials.<sup>9</sup> Overall, the decreased risk of mortality associated with nutritional support found in the present analysis suggests that malnutrition is a modifiable risk factor for mortality, with nutritional support being an effective treatment option.

These findings differ from those of other recent reviews of nutritional support. A recent Cochrane review<sup>10</sup> did not find a positive association between nutritional support and outcomes in hospitalized adults at nutritional risk. However, this study included a larger variety of patients, including intensive care unit and surgical patients, who may have specific nutritional and metabolic needs. It should be noted that patients treated in intensive care units tend to be highly catabolic, and it is likely that nutritional support would not alter this process. On the other hand, nutritional support in non-critically ill medical patients who are malnourished may result in increased protein synthesis and increased lean body mass. The Cochrane review<sup>10</sup> also included a wider range of interventions, including parenteral nutrition, which may be associated with a higher risk for adverse outcomes. Furthermore, the literature searches were conducted in February 2016, which excludes 2 recent, large, nutritional support RCTs of medical inpatients at nutritional risk (the EFFORT trial,<sup>38</sup> published in 2018 with 2028 patients; and the NOURISH trial,<sup>36</sup> published in 2016 with 652 patients). Inclusion of these trials may also alter the overall interpretation of this present study.

One could postulate that nutritional support would have limited the loss of lean body mass, thereby improving muscle strength and functional outcomes, but this finding was not observed in the present study. However, only 5 studies<sup>16,18,19,38,41</sup> assessed functional outcomes, defined by the Barthel index score at follow-up (eFigure 4 in the [Supplement](#)). The absence of any association between nutritional support and improved functional outcomes may be attributable to the methods used in the few studies that assessed this outcome and the relatively short duration of nutritional support (or time for the assessment of functional status).

Of importance, in the present analysis, nutritional support was associated with more benefits in the subgroup of patients with established malnutrition vs than in the patients at nutritional risk, particularly for hospital readmissions, functional outcomes, LOS, and mortality, for which the differences between groups were statistically significant or more pronounced. This finding highlights the importance of using validated methods to assess patients' nutritional status to identify those who are more likely to benefit from nutritional support. A team approach including nurses, dietitians, and physicians may provide a solution to the problem of identifying and appropriately addressing malnutrition in the hospital setting.

In the context of increasing health care costs, the significant reduction in hospital readmissions observed on the overall analysis and the reduction in LOS shown in the subgroup of patients with established malnutrition may be particularly relevant for policy makers. If these findings are borne out in subsequent trials, given that approximately 30% of general medical inpatients meet the

criteria for malnutrition,<sup>2</sup> patient-specific nutritional interventions may result in substantial cost and hospital utilization reductions in addition to the mortality benefits (eg, in an analysis of inpatient use of oral nutritional supplements in more than 1 million participants<sup>42</sup>). Future studies should focus on the cost-effectiveness of providing nutritional support interventions for medically ill patients. The evaluation of other patient-centered outcomes, such as quality of life, should also be explored in more detail.

### Limitations

This study has limitations. Several of the included studies had a high or unknown risk of bias, small sample sizes, and short study duration (ie, limited to the hospital stay). Malnutrition starts in the community (the patient is identified as being malnourished on admission to the hospital) and does not end at the hospital discharge; therefore, the causes of malnutrition in the community need to be explored, and nutritional support should be continued after hospital discharge. In addition, heterogeneity was observed with regard to the types of interventions and the control groups. Some trials were placebo-controlled efficacy trials focusing on the effect of specific products, whereas others were effectiveness trials comparing complex interventions with routine care, which may vary across health care settings.

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### Conclusions

This updated systematic review and meta-analysis found that use of nutritional support interventions was associated with clinically significant improvements of important clinical outcomes in the medical inpatient population, in whom malnutrition is highly prevalent.<sup>43</sup> This analysis supports the current practice guidelines issued by the European Society for Clinical Nutrition and Metabolism (ESPEN)<sup>4</sup> and the American Society for Parenteral and Enteral Nutrition (ASPEN),<sup>8</sup> advocating a proactive, screening-based approach for initiating nutritional support during the hospital stay of medical inpatients who are malnourished or at nutritional risk.

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### ARTICLE INFORMATION

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**Acquisition, analysis, or interpretation of data:** All authors.

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#### SUPPLEMENT.

**eAppendix.** Search Strategy Used in MEDLINE

**eFigure 1.** Flow Chart of Studies' Selection

**eFigure 2.** Risk of Bias Overall and Stratified by Trial

**eFigure 3.** Forest Plot Comparing Nutritional Intervention vs. Control for Infection Stratified by Publication Year

**eFigure 4.** Forest Plot Comparing Nutritional Intervention vs. Control for Functional Outcome Stratified by Publication Year

**eFigure 5.** Forest Plot Comparing Nutritional Intervention vs. Control for Length of Stay Stratified by Publication Year

**eFigure 6.** Forest Plot Comparing Nutritional Intervention vs. Control for Daily Energy Intake Stratified by Publication Year

**eFigure 7.** Forest Plot Comparing Nutritional Intervention vs. Control for Daily Protein Intake Stratified by Publication Year

**eFigure 8.** Forest Plot Comparing Nutritional Intervention vs. Control for Weight Change Stratified by Publication Year

**eTable.** Adherence to Study Protocol

**eReferences.**



Invited Commentary | Nutrition, Obesity, and Exercise

# Nutritional Support Among Medical Inpatients—Feed the Cold (and Malnourished) and Starve the Febrile

Paul E. Marik, MD

Acute illness results in a severe catabolic state with marked proteolysis and loss of lean body mass. Loss of lean body mass has profound consequences, resulting in marked functional disability and increasing the risk of falls, bone fractures, and generalized frailty. The consequences of acute illness on functional outcomes are best illustrated by the study of Herridge and colleagues,<sup>1</sup> who followed 109 patients who had survived acute respiratory distress syndrome. In their study, patients had lost 18% of their baseline body weight by the time they were discharged, and all complained of weakness and fatigue; at 12 months, the distance walked in 6 minutes was 66% of that predicted. Furthermore, after 5 years of follow-up, functional ability had not improved over values at 1 year.

Early nutrition is widely believed to limit the catabolism of acute illness and improve patient outcomes, including functional status. Nutritional support is, therefore, considered an essential component of the management of all acutely ill hospital inpatients, with current practice for both patients in the intensive care unit (ICU) and those not in the ICU emphasizing early and targeted nutritional support. However, does the evidence support these practices? Recently a number of high-quality trials<sup>2,3</sup> of critically ill patients have failed to demonstrate improved patient outcomes with early targeted nutritional support. Indeed, the study by Casaer et al<sup>4</sup> demonstrated that early parenteral nutrition achieving high protein and caloric targets was associated with a worse outcome than delayed parenteral nutrition. Similarly, malnourished critically ill patients may be harmed by early aggressive enteral nutrition.

Can the unequivocal evidence from critically ill patients be extrapolated to noncritically ill hospital inpatients (non-ICU), particularly those of borderline baseline nutritional status? This question is addressed by the pivotal systematic review and meta-analysis by Gomes and colleagues.<sup>5</sup> This study demonstrates that, among medical inpatients who are malnourished or at nutritional risk, targeted nutritional support provided during hospitalization is associated with significantly lower rates of mortality and nonelective hospital readmissions, as well as higher energy and protein intakes with greater weight gain.

There are a number of possible biological explanations for the contrasting benefits of nutritional support for inpatients in the ICU and those not in the ICU. Distinct metabolic pathways are involved in the synthesis and degradation of muscle. In critical illness, loss of muscle mass results from an imbalance between muscle proteolysis and protein synthesis, with proteolysis overwhelming an inadequate synthetic response. Forkhead box O is a family of transcriptional factors that plays a major role in muscle wasting, primarily by increasing expression of muscle RING-finger 1 and muscle atrophy F-box.<sup>6</sup> Forkhead box O is activated by inflammation and sepsis. It is likely that ongoing and persistent inflammation in critically ill patients results in a catabolic process with muscle proteolysis that cannot be reversed by high-quality nutritional support. However, for inpatients without ongoing inflammation, the provision of high-quality nutritional support (especially with increased leucine) will favor protein synthesis over proteolysis. Furthermore, nutritional intake suppresses autophagy with inadequate clearance of pathogens and damaged cells, and this may theoretically be harmful in the setting of acute infections.

There is another intriguing possibility to explain the differences in outcomes between the studies of the critically ill patients in the ICU and those in the non-ICU wards. In the studies included in the meta-analysis by Gomes et al,<sup>5</sup> the overwhelming majority of patients received oral nutritional

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supplements (ONS)—that is, they received supplemental nutrition by mouth intermittently during the course of the day. This is illustrated by the 2 largest studies included in the meta-analysis. In the study by Deutz et al,<sup>7</sup> all the patients in the intervention group received a specialized ONS (high-protein,  $\beta$ -hydroxy- $\beta$ -methylbutyrate formulation). In the study by Schuetz et al,<sup>8</sup> 91% of patients in the treatment group received ONS in combination with enriched hospital nutrition. In that study, enteral nutrition was used for 8 patients (0.8%) and parenteral nutrition was used for 12 patients (1.1%) in the intervention group. These findings contrast sharply with all the studies performed of critically ill patients, for whom nutrition was provided as either continuous enteral feeding (via a feeding tube or nasogastric tube) or a continuous intravenous infusion of parenteral nutrition. It is critically important to recognize that no species on this planet eats continuously (day and night), and such an evolutionary design would seem absurd. The alimentary tract and metabolic pathways of humans appear to have evolved for intermittent ingestion of nutrients a few times a day.<sup>6</sup> Humans have evolved as intermittent meal eaters and are not adapted to a continuous inflow of nutrients; normal physiology appears to be altered when this approach is adopted. Continuous, as opposed to intermittent, enteral feeding likely limits protein synthesis.<sup>6</sup> Muscle protein synthesis requires a pulsatile increase in branch-chain amino acids (particularly leucine) with or without concomitant pulses in insulin levels. Animal data demonstrate that muscle protein synthesis following a meal is rapid (within 30 minutes) and sustained for about 2 hours but then declines toward baseline in parallel with the postprandial changes in circulating insulin and amino acids.<sup>9</sup> Bohé and colleagues<sup>10</sup> measured the latency and duration of the stimulation of human muscle protein synthesis during a continuous infusion of amino acids in humans. The rate of muscle protein synthesis increased after 30 minutes, reached a peak at 2 hours, and rapidly returned to baseline levels by 4 hours despite continuous amino acid availability. These findings are supported by experimental studies where the continuous supply of amino acids has been demonstrated to blunt protein synthesis.<sup>6</sup>

The findings of the systematic review and meta-analysis by Gomes et al<sup>5</sup> are important. They suggest that all hospital inpatients should undergo screening using a validated nutrition-screening tool. Those patients at nutritional risk should receive individualized nutritional support including the provision of a high-quality ONS. The optimal “whey” to feed critically ill patients in the ICU has yet to be determined; however, less may be more.<sup>6</sup>

## ARTICLE INFORMATION

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