Nutritional Support and Outcomes in Malnourished Medical Inpatients
A Systematic Review and Meta-analysis

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IMPORTANCE During acute illness, nutritional therapy is widely used for medical inpatients with malnutrition or at risk for malnutrition. Yet, to our knowledge, no comprehensive trial has demonstrated that this approach is effective and beneficial for patients.

OBJECTIVE To assess the effects of nutritional support on outcomes of medical inpatients with malnutrition or at risk for malnutrition in a systematic review of randomized clinical trials (RCTs).

DATA SOURCES The Cochrane Library, MEDLINE, and EMBASE. The study dates were October 5, 1982, to April 30, 2014, in various (mostly European) countries. The dates of our analysis were March 10, 2015, to September 16, 2015.

STUDY SELECTION Based on a prespecified Cochrane protocol, we systematically searched RCTs investigating the effects of nutritional support (including counseling and oral and enteral feeding) in medical inpatients compared with a control group.

DATA EXTRACTION Two reviewers extracted data on study characteristics, methods, and outcomes. Disagreement was resolved by consensus.

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

RESULTS We included 22 RCTs with a total of 3736 participants. Heterogeneity across RCTs was high, with overall low study quality and mostly unclear risk of bias. Intervention group patients significantly increased their weight (mean difference, 0.72 kg; 95% CI, 0.23-1.21 kg), caloric intake (mean difference, 397 kcal; 95% CI, 279-515 kcal), and protein intake (mean difference, 20.0 g/d; 95% CI, 12.5-27.1 g/d) compared with control group patients. No differences between intervention group patients and control group patients were found with respect to mortality (9.8% vs 10.3%; odds ratio [OR], 0.96; 95% CI, 0.72-1.27), hospital-acquired infections (overall, 6.0% vs 7.6%; OR, 0.75; 95% CI, 0.50-1.11), functional outcome (mean Barthel index difference, 0.33 point; 95% CI, −0.88 to 1.55 points), or length of hospital stay (mean difference, −0.42 days; 95% CI, −1.09 to 0.24 days). Nonelective readmissions were significantly decreased by the intervention (20.5% vs 29.6%; risk ratio, 0.71; 95% CI, 0.57-0.87).

CONCLUSIONS AND RELEVANCE In medical inpatients, nutritional support increases caloric and protein intake and body weight. However, there is little effect on clinical outcomes overall except for nonelective readmissions. High-quality RCTs are needed to fill this gap.

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Malnutrition is common in hospitalized patients and is associated with detrimental metabolic consequences such as muscle wasting.1,2 Furthermore, malnutrition per se is associated with higher mortality and morbidity, increased infections, and prolonged length of hospital stay.3–5 This evidence explains the current clinical approach of providing nutritional support early as a strategy to treat malnutrition and its associated adverse outcomes.6

Recent high-quality, large-scale randomized clinical trials (RCTs) from critical care have challenged the approach of using nutritional therapy in the acute phase of illness in unselected patients.7 Deliberate effects of aggressive overfeeding were found in one large trial,8 and no benefit of enteral feeding over permissive underfeeding was found in another recent trial.9 Furthermore, the provision of parenteral nutrition to critically ill adults compared with standard care did not reduce mortality in an additional critical care trial.10 Given these results from critical care, the approach of using nutritional therapy in the acute phase of illness in medical inpatients with malnutrition or at risk for malnutrition needs to be challenged.

To our knowledge, no comprehensive trial or meta-analysis has investigated clinical benefit or harm associated with nutritional support in the medical inpatient population. Available meta-analyses focus on different study questions and patient populations, including enteral nutrition in critical care or perioperative patients,11 protein and energy supplementation in the elderly,12 nutritional support in liver disease,13 and nutritional supplementation after hip fracture in older individuals.14 Therefore, whether the use of nutritional therapy in medical inpatients has beneficial effects on outcomes such as mortality, hospital-acquired infections, nonelective readmissions, and functional outcome remains unclear.

To fill this knowledge gap, we conducted a comprehensive systematic review and meta-analysis of RCTs. We assessed the effects of nutritional support (oral or enteral) on outcomes in medical inpatients with malnutrition or at risk for malnutrition.

**Methods**

**Eligibility Criteria**

A previously published Cochrane protocol outlines our study methods.15 We included RCTs and quasi-RCTs that randomized noncritically ill medical inpatients with malnutrition or at risk for malnutrition to a nutritional therapy intervention or a control group.

We included RCTs that established risk for malnutrition based on body mass index, the presence of a medical condition strongly associated with malnutrition occurring during hospital stay, or the use of a nutritional assessment or screening tool (eg, Subjective Global Assessment, Malnutrition Universal Screening Tool, or Nutritional Risk Screening). Medical inpatients were defined as patients hospitalized in medical wards of acute care institutions, including geriatrics, gastroenterology, cardiology, pneumology, general internal medicine, infectious diseases, nephrology, and oncology.

Trials focusing on patients hospitalized in critical care wards or residing in nursing homes or long-term facilities, as well as outpatients, were not eligible for this analysis. In addition, trials focusing on surgical patients were also not eligible except for those reporting the results of mixed medical and surgical patient populations when the medical population was not reported separately. We also excluded trials focusing on patients with pancreatitis because of important differences in the nutritional concept of this disease compared with other acute medical illnesses (ie, withholding oral or enteral nutrition until days 3–5 is recommended in mild and moderate forms of acute pancreatitis).16

**Types of Interventions**

We included trials with interventions consisting of any type of nutritional support except for parenteral nutrition. For the comparator groups, we defined the following types of interventions: (1) dietary advice (changes in the organization of nutritional care [eg, support of dieticians or health care assistants, training in nutritional care for medical personnel, implementation of nutritional care pathways or protocols, and feeding assistance]), (2) food fortification (snacks between meals and increased caloric and protein intake), (3) oral feeding in addition to meals (any type of oral nutritional supplement), and (4) enteral feeding (any type of total or partial enteral [tube] feeding). In our primary analysis, we included any of the above nutritional strategies or any combination of them. There was no restriction regarding the minimum duration of the intervention.

We applied no restrictions with respect to control group treatments. We defined the following comparator groups: (1) no support, (2) usual care (possibly providing dietary advice or oral nutritional supplement), and (3) placebo treatment.

**Outcomes**

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 4–6 months after randomization). Secondary outcomes during follow-up included the following: hospital-acquired infections (with a new infection diagnosis after study inclusion until hospital discharge or at follow-up), nonelective readmissions (defined as any hospital or emergency department visit until follow-up), functional outcome (assessed by the Barthel index as an absolute measure at follow-up), length of hospital stay (defined as the time from hospital admission or randomization to discharge), and adverse events (defined based on the definition used in the original RCT). Other metabolic outcomes included body weight change (in kilograms), measured from study inclusion until hospital discharge or at follow-up, and the mean daily caloric intake (in kilocalories) and daily protein intake (in grams) during the intervention period. We also gathered information about adherence to the nutritional intervention and the study protocol.

**Search Strategy**

We searched 3 electronic databases, including the Cochrane Library, MEDLINE, and EMBASE, from the inception of each database to December 11, 2014. Search terms included extensive controlled vocabulary and Medical Subject Headings for (RCTs) AND (malnutrition) AND (adults) AND (nutritional therapy). We reviewed bibliographies of review articles and eli-
gible trials and searched the clinicaltrials.gov registry for on-
going or unpublished trials. We also contacted experts work-
ing in the field of malnutrition to identify additional or unpub-
lished trials.

Study Selection
Two reviewers (M.R.B. and P.Z.B.Y.) independently screened titles and abstracts of articles and full texts of any title or abstract deemed potentially eligible by either reviewer. We re-
solved any discrepancies through consensus or recourse to a third reviewer (P.S.).

Risk-of-Bias Assessment of Individual Studies
As recommended by the Cochrane Collaboration, 2 reviewers (M.R.B. and L.B.) independently assessed the risk of bias asso-
associated with individual RCTs.17 We used the following crite-
ria: (1) random sequence generation (selection bias); (2) ran-
domization concealment (selection bias); (3) blinding (per-
formance bias and detection bias), separated for blinding of par-
ticipants and personnel, and blinding of outcome as-
essment; (4) incomplete outcome data (attrition bias); (5) se-
lecting reporting (reporting bias); and (6) other bias. Furthi-
more, the quality of outcomes was assessed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.18

Data Extraction
For studies that fulfilled inclusion criteria, 2 reviewers (M.R.B. and P.Z.B.Y.) independently abstracted key participant and in-
tervention characteristics and reported data on efficacy out-
comes using a standardized data extraction template. Any dis-
agreements were resolved by discussion or by consulting a third reviewer (P.S.). Continuous outcomes were most often re-
ported as the absolute mean change from baseline, which we used directly to pool data. The absolute mean change was cal-
culated in case continuous data were reported as preinterven-
tion and postintervention measures or percentage change. If standard deviations were missing and we did not receive in-
formation from study authors, we assumed missing standard de-
viations to be the mean (SD) of those studies in which this in-
formation was reported. We investigated the effect of this as-
sumption by sensitivity analysis.

We maximized the yield of information by collating all the available data in the event of multiple publications, companion documents, or multiple reports and used the most com-
plete data set aggregated across all available publications of an RCT. In case of doubt, we gave priority to the publication reporting the longest follow-up.

Data Synthesis and Analysis
We expressed dichotomous data as odds ratios (ORs) or risk ratios with 95% CIs. We expressed continuous data as the mean differences with 95% CIs. Data were pooled using a random-
effects model.

Assessment of Heterogeneity and Publication Bias
In the event of substantial clinical, methodological, or statis-
tical heterogeneity, we did not pool the effect estimates in a

meta-analysis. We identified heterogeneity (inconsistency) through visual inspection of the forest plots and by using a stan-
dard χ² test with a significance level of α = .10. In view of the low power of this test, we also considered the I² statistic, which quantifies inconsistency across studies, to assess the effect of heterogeneity on the meta-analysis.19 An I² statistic of 50% or more indicates a considerable level of heterogeneity.

We used visual inspection of funnel plots to assess publi-
cation bias. Owing to several possible explanations for funnel plot asymmetry, we interpreted these results cautiously.20

We also performed a predefined subgroup analysis stratified by degree of malnutrition (ie, established malnu-
trition vs risk for malnutrition). Furthermore, we performed additional exploratory subgroup analyses investigating adherence to the study protocol, mortality risk in control group patients (<10% vs ≥10%), and route of feeding (oral vs enteral).

Results
Systematic Search
Our systematic search identified 4393 titles and abstracts of potentially eligible studies from electronic databases and one additional record through contact with experts. After re-
moval of duplicates, 2673 records were screened, and 44 full texts were assessed for eligibility. Of these results, 22 RCTs (with a total of 3736 patients) were included in the final meta-
analysis. A flowchart is shown in Figure 1.

Most of the included RCTs were single-center studies and involved heterogeneous adult medical or mixed medical and surgical inpatients. The study dates were October 5, 1982, to April 30, 2014, in various (mostly European) countries. The dates of our analysis were March 10, 2015, to September 16, 2015. Interventions were mainly oral feeding strategies, with 2 trials also providing enteral feeding to the intervention group. Nutritional counseling was part of the intervention in most studies. Control group patients were mostly treated based on usual care. Five trials used a placebo-controlled interven-
tion. Additional characteristics of the included RCTs are sum-
marized in Table 1.

Risk-of-Bias Assessment
We investigated performance bias, detection bias, and attri-
tion bias separately for objective and subjective outcome mea-
sures in each individual trial as recommended by the Cochr-
ane Collaboration (eAppendix in the Supplement). Appropriate random sequence generation and randomization conceal-
ment were used in less than half of all trials, with many trials not reporting procedural details. There was a low or unclear risk of bias in most trials except for performance bias because masking of participants and personnel to the nutritional inter-
ventions was not done in most studies. Also, attrition bias was high or unclear because of incomplete outcome reporting in many studies. The quality of the evidence according to the GRADE method to assess the effects of nutritional sup-
port on mortality was low and was low to very low for all other outcomes.
Primary Outcome

Table 2 summarizes outcomes in the overall population and in subgroups. For the primary end point, 14 studies reported all-cause mortality, ranging from 4% to 52% in the various RCTs. In the overall analysis, death occurred in 9.8% (133 of 1361) of intervention group patients compared with 10.3% (144 of 1395) of control group patients (OR, 0.96; 95% CI, 0.72-1.27). We found low heterogeneity among trials ($I^2 = 8\%$, $P = .37$) (Figure 2). We then stratified the results based on the type of intervention. There was no significant association between nutritional therapy and mortality in any of the subgroups based on the type of nutritional therapy. In the 4 trials comparing oral feeding with placebo, the effect estimates tended to be worse for the nutritional intervention (OR, 1.52; 95% CI, 0.96-2.39). In the 3 trials comparing oral nutrition alone with usual care, the effect estimates tended to indicate benefit from nutritional therapy (OR, 0.61; 95% CI, 0.35-1.05).

Secondary Outcomes

Thirteen RCTs reported the length of hospital stay, and 6 RCTs reported nonelective readmissions. The readmission rate was significantly lower in intervention group patients compared with control group patients (20.5% vs 29.6%; risk ratio, 0.71; 95% CI, 0.57-0.87), with overall low heterogeneity among trials ($I^2 = 0\%$) (Figure 3). Overall, the length of hospital stay was not significantly shorter in intervention group patients compared with control group patients (13.0 vs 10.8 days; difference, −0.42 days; 95% CI, −1.09 to 0.24 day). This finding was also true for most individual trials, with overall low heterogeneity among trials ($I^2 = 0\%$) (Table 2 and eAppendix in the Supplement).

No significant effect was found for infections in any individual trial or in the overall analysis (overall, 6.0% vs 7.6%; OR, 0.75; 95% CI, 0.50-1.11), with low heterogeneity ($I^2 = 0\%$) (eAppendix in the Supplement). Four RCTs reported functional outcome with measurement of the Barthel index at follow-up. There was no significant difference in the Barthel index between intervention group patients and control group patients in the overall analysis (mean Barthel index difference, 0.33 points; 95% CI, −0.88 to 1.55 points). Heterogeneity among these trials was high ($I^2 = 78\%$). Stratification of the 4 RCTs by comparison category explained the identified heterogeneity, and there was no evidence of any difference between groups except for one RCT comparing oral feeding alone vs no support. In that RCT, a significant difference in the Barthel index of 4 points (95% CI, 1.69-6.31 points) was found, suggesting better functional outcome in patients with oral feeding. Test for interaction indicated a statistically significant result ($P = .004$).

For adverse outcomes associated with nutritional therapy, trials showed high heterogeneity. Therefore, we did not further include adverse outcomes in the meta-analysis.
<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>Population</th>
<th>Sample Size</th>
<th>Control Group</th>
<th>Intervention Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broqvist et al, 2004</td>
<td>Sweden</td>
<td>Congestive heart failure</td>
<td>21</td>
<td>Normal hospital food and between meals, with 500 mL of ONS daily containing 30 g of protein and 550 kcal</td>
<td>Usual care</td>
</tr>
<tr>
<td>Bunout et al, 2004</td>
<td>Chile</td>
<td>Alcohol liver disease</td>
<td>36</td>
<td>Oral diet, including 50 kcal/kg/d, 1.5 g of protein per kg daily, casein-based product</td>
<td>Usual diet</td>
</tr>
<tr>
<td>Feldblum et al, 2011</td>
<td>Israel</td>
<td>Hospitalized acutely ill older patients</td>
<td>80</td>
<td>Individual nutritional treatment, 237 mL containing 12.6 g of fat, 13 g of protein, and 21 g of protein daily</td>
<td>Usual care</td>
</tr>
<tr>
<td>Gariballa et al, 2006</td>
<td>England</td>
<td>Patients ≥75 y and at risk for undernutrition</td>
<td>210</td>
<td>Standard hospital diet, no supplements</td>
<td>Usual care</td>
</tr>
<tr>
<td>Gazzotti et al, 2011</td>
<td>Italy</td>
<td>Malnourished elderly</td>
<td>81</td>
<td>Protein-enriched small dishes supplementary to standard food service, ONS, or snacks</td>
<td>Usual care</td>
</tr>
<tr>
<td>Hogarth et al, 1996</td>
<td>England</td>
<td>Elderly medical inpatients</td>
<td>25</td>
<td>1. Daily 750 mL of oral glucose supplement (540 kcal) and capsules containing vitamins A (8000 U), B1 (15 mg), B2 (15 mg), B3 (50 mg), B6 (10 mg), and C (500 mg) during 1 mo 2. Daily 750 mL of oral glucose supplement (540 kcal) and placebo capsules during 1 mo</td>
<td>Usual care</td>
</tr>
<tr>
<td>Holyday et al, 2012</td>
<td>Australia</td>
<td>Older patients, depression</td>
<td>143</td>
<td>Individual modification of hospital meals (fortification), nutritional supplements</td>
<td>Usual care</td>
</tr>
<tr>
<td>James, 1982</td>
<td>England</td>
<td>Acutely ill older patients</td>
<td>86</td>
<td>1. ONS 566 kcal/d, 23.9 g of protein daily 2. Nocturnal tube feeding (nasogastric tube), additional intake of 84 kcal/d and 29.5 g of protein daily</td>
<td>Usual care</td>
</tr>
<tr>
<td>McWhirter and Pennington, 1996</td>
<td>England</td>
<td>Hospitalized patients</td>
<td>82</td>
<td>Usual hospital screening and nutritional counseling on demand</td>
<td>Usual care</td>
</tr>
<tr>
<td>Neelemaat et al, 2015</td>
<td>Netherlands</td>
<td>Malnourished elderly</td>
<td>252</td>
<td>Energy-enriched and protein-enriched diet, 2 additional servings of an ONS, or snacks</td>
<td>Usual care</td>
</tr>
<tr>
<td>Ollenschläger et al, 1992</td>
<td>Germany</td>
<td>Patients with acute leukemia</td>
<td>38</td>
<td>Nutritional screening of all patients, clinical nutritional plan initiated by the nurse manager</td>
<td>Usual care</td>
</tr>
<tr>
<td>Ollenschläger et al, 2003</td>
<td>Germany</td>
<td>Patients with acute leukemia</td>
<td>38</td>
<td>Nutritional screening of all patients, clinical nutritional plan</td>
<td>Usual care</td>
</tr>
<tr>
<td>Ollenschläger et al, 2004</td>
<td>Germany</td>
<td>Unwell elderly patients</td>
<td>56</td>
<td>Usual hospital screening and nutritional counseling</td>
<td>Usual care</td>
</tr>
<tr>
<td>Ollenschläger et al, 2005</td>
<td>Germany</td>
<td>Hospitalized patients</td>
<td>72</td>
<td>Usual hospital screening and nutritional counseling</td>
<td>Usual care</td>
</tr>
</tbody>
</table>

**Abbreviation:** ONS, oral nutritional supplement.
Table 2. Outcomes Overall and in Subgroups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>Risk Ratio (95% CI)</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mortality</td>
<td>Hospital-</td>
<td>Risk Maintenance</td>
</tr>
<tr>
<td>Overall Population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention group, events/total (%)</td>
<td>133/1361 (0.98)</td>
<td>48/802 (6.0)</td>
<td>10/516 (20.5)</td>
</tr>
<tr>
<td>Control group, events/total (%)</td>
<td>144/1395 (10.3)</td>
<td>63/812 (7.8)</td>
<td>14/497 (29.6)</td>
</tr>
<tr>
<td>Overall estimate</td>
<td>0.96 (0.72 to 1.27)</td>
<td>0.75 (0.50 to 1.11)</td>
<td>0.71 (0.57 to 0.87)</td>
</tr>
<tr>
<td>Overall Population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I² Test for subgroup difference, %</td>
<td>49</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Sensitivity Analyses**

In sensitivity analyses, we stratified trials by degree of malnutrition, control group mortality, adherence to nutrition protocols, and route of nutritional support (oral vs enteral feeding) (eAppendix in the Supplement). There were suggestions of larger benefits from nutritional therapy for the subgroup of patients with established malnutrition compared with patients at risk for malnutrition, particularly for mortality, functional outcome, and length of hospital stay. For patients having higher mortality risk (≥10%) compared with patients having lower mortality risk (<10%), the effects tended to be larger, with no statistically significant results in subgroup difference tests. Stratification by protocol adherence found more daily caloric and protein intake, as well as more weight gain, in trials with high adherence, but clinical outcomes were similar compared with the overall analysis.

**Discussion**

The findings of this first comprehensive systematic review and meta-analysis to date focusing on the acutely ill medical inpatients...
patient population with established malnutrition or at risk for malnutrition are 3-fold. First, 22 RCTs met our inclusion criteria. We found considerable heterogeneity across trials for the type of intervention and control group, as well as the clinical setting, and mostly low study quality, with often unclear risk of bias. Second, overall and in most individual trials, nutri-

M-H indicates Mantel-Haenszel.

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Nutritional support was significantly associated with higher daily caloric and protein intake, most likely explaining the detected mean weight gain difference of 0.72 kg compared with controls. Third, there was little effect on clinical outcomes overall, including mortality, hospital-acquired infections, and functional outcome. Still, in the overall analysis, nonelective readmissions were significantly lower among the intervention group. Fourth, the length of hospital stay tended to positively affect the recurrence of illnesses in medical patients, suggesting that improved nutritional status might optimize the length of hospital stay needed to treat for readmission frequency.

Interestingly, the frequency of hospital-acquired infections was also lower in the intervention group. In addition, the number of patients with established malnutrition, the length of hospital stay tended to be shorter in the intervention group. Nutritional support using oral nutrition (mainly via oral nutritional supplement) or enteral feeding is one of the most common interventions in medicine. Still, there is a lack of comprehensive trial data demonstrating its beneficial effects on outcomes in the general medical inpatient population. This paucity might explain why no standard nutritional algorithm for use in polymorbid medical inpatients with malnutrition or at risk for malnutrition exists today, to our knowledge. Most guidelines from the American Society for Parenteral and Enteral Nutrition and the European Society for Parenteral and Enteral Nutrition focus on specific medical disciplines (eg, individuals with cancer, geriatric patients, and those with sepsis) or organs (eg, renal failure and wound healing) but give little guidance on polymorbid patients. Also, current recommendations are mostly based on pathophysiological considerations and evidence from smaller trials. As a consequence, general internists caring for polymorbid inpatients may have insufficient evidence for informed decision making in individual patients for optimal use of nutritional therapy. In light of potential harmful effects of nutritional therapy, as demonstrated by the meta-analysis by Starke et al.,

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio M-H, Random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteral nutrition with dietary advice vs usual care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somanchi et al.43 2011</td>
<td>8 106</td>
<td>14 83</td>
<td>0.45 (0.20-1.02)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>8 106</td>
<td>14 83</td>
<td>0.45 (0.20-1.02)</td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: z = 1.92 (P = .05)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Oral feeding alone vs placebo | | |
| Gazzotti et al.,25 2003 | 4 34 | 3 35 | 1.37 (0.33-5.68) |
| Subtotal (95% CI) | 4 34 | 3 35 | 1.37 (0.33-5.68) |
| Heterogeneity: not applicable | | |
| Test for overall effect: z = 0.44 (P = .66) | | |

| Oral feeding with dietary advice vs usual care | | |
| Holyday et al.,26 2012 | 8 67 | 8 71 | 1.06 (0.42-2.66) |
| Starke et al.,40 2011 | 17 64 | 28 61 | 0.58 (0.35-0.94) |
| Subtotal (95% CI) | 25 131 | 36 132 | 0.69 (0.40-1.18) |
| Heterogeneity: I² = 0.0%; χ² = 1.31 (P = .25); I² = 2.4% | | |
| Test for overall effect: z = 1.36 (P = .17) | | |
| Total (95% CI) | 106 516 | 147 497 | 0.71 (0.57-0.87) |
| Heterogeneity: I² = 0.0%; χ² = 3.57 (P = .61); I² = 0% | | |
| Test for subgroup difference: χ² = 2.14 (P = .17); I² = 0% | | |

M-H indicates Mantel-Haenszel.

Calculated and approximated from readmission rate.

Calculated and approximated from readmission frequency.
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strated in the critical care patient population, a reappraisal of how nutritional therapy should be used in non–critically ill medical inpatients is required. Therefore, this systematic review and meta-analysis is important to give a comprehensive overview of the expected effects of different nutritional interventions on metabolic and clinical outcomes of medical inpatients. Our study differs from previous meta-analyses because we did not limit trials to specific interventions (eg, oral nutritional supplement only or enteral feeding) or patient populations. We focused on a broad medical inpatient population but excluded surgical and critical care patients, those with pancreatitis, and individuals with less acute disease residing in long-term facilities, where the effects of nutritional therapy may differ from the acute care setting.

Most important, data have suggested that nutritional therapy can also negatively affect clinical outcomes if used early in sick patients. During the acute phase of illness, the body mobilizes substrates from muscle and fat tissue to match increases in resting energy expenditure. Exogenous calories then no longer inhibit gluconeogenesis. Therefore, excessive nutrition during the acute phase of illness can induce occult overfeeding and may interact with autophagy. How caloriesthennolongerinhibitgluconeogenesis. Therefore, extensive care unit for whom enteral nutrition alone was ing (3 days after admission) in severely ill patients in the intensive care therapy can also negatively affect clinical outcomes if used early in sick patients, which is reassuring. Yet, individual trials in our analysis were not powered for mortality, and trial quality was low, with often unclear risk of bias. Therefore, harmful effects cannot be excluded at this point, and larger conclusive trials are needed. Also, there is a lack of cost-benefit data for our patient population, and costs may still outweigh clinical benefits such as lower readmission rates.

Data from critical care cannot be unconditionally be extrapolated to medical inpatients, who have a lower degree of disease severity. Still, the conflicting observations regarding the benefits of early nutritional support in critically ill patients begs an additional question and requires additional studies to better define the optimal approach in medical inpatients. As highlighted by this systematic search and meta-analysis, the current lack of guideline recommendations for nutritional support in general medical inpatients might be mainly explained by the paucity of high-quality studies providing evidence on the efficacy, safety, and cost-effectiveness of this strategy. Given the complex nature of nutritional therapy regarding the type of nutrition (eg, the amount and type of protein and the total amount of calories), method of delivery (oral vs enteral), timing, and adherence, a comprehensive effectiveness research trial that includes a large and diverse patient population is needed to demonstrate which patients benefit most from nutritional therapy. In light of the results of our subgroup analysis, patients with established malnutrition and higher-acuity patients may be more likely to have positive results. In a second step, trials investigating specific nutritional aspects are needed to delineate which nutritional components have positive influences on specific medical conditions (eg, immunonutrition).

Our study has several limitations. The included RCTs were mostly older studies randomizing small numbers of patients. There was considerable heterogeneity with respect to treatment modalities and patient populations as a result of using wide inclusion criteria and not limiting the trials to specific interventions or patient populations. Furthermore, according to the GRADE method, the quality of the evidence was low to very low for most outcomes. Finally, the risk-of-bias analysis revealed unclear risks for most biases and high risk for performance bias and attrition bias. In addition, the wide 95% CIs for most patient-relevant clinical outcomes preclude any firm conclusions regarding the effects of nutritional support. Yet, our findings call for conducting more high-quality RCTs covering this important topic.

Conclusions

For the medical inpatient population, our results show that nutritional interventions increase daily caloric and protein intake, as well as body weight. Yet, there is little effect of nutritional support on clinical outcomes in malnourished medical inpatients overall except for a significant reduction in non-elective admissions and a suggestion of shorter length of hospital stay. High-quality RCTs are needed to provide more definite conclusions.
REFERENCES


Malnutrition lurks in the background, if not the forefront, of hospitalized patients. More than one-third of patients are seen in the hospital with varying degrees of malnutrition, and far too many experience further nutritional deterioration during their stay and convalescence. We have become more alert to this challenge ever since the shocking revelations in 1974 by Butterworth that the issue of nutrition of inpatients was frequently neglected. Well before that, suboptimal nutrition states were closely associated with poor outcomes. However, 40 years after our eyes were opened to this long-ignored issue, we struggle to identify appropriate patients and efficacious nutritional interventions.

Malnutrition has been defined as a subacute or chronic state of nutrition in which a combination of varying degrees of overnutrition or undernutrition and inflammatory activity have led to deleterious changes in body composition and diminished function. While early and mild effects on appetite, intake, and metabolism are beneficial physiological responses in a host undergoing an inflammatory challenge, prolongation of these effects can eventually lead to impaired defenses and function, with worse outcomes. Nutritional interventions have the potential to offset some of the excessive losses and deficiencies but can also result in undesired consequences if delivered at the wrong time, in the wrong form, or by the wrong way. Nowhere has this dilemma been more clearly demonstrated than in critical care populations receiving overzealous deliveries of glucose, fat, and other nutrients via the parenteral route, resulting in hyperglycemia, immunosuppression, and negative outcomes. Most of our current knowledge and subsequent recommendations for nutritional intervention have come from studies of critical care or surgical populations, among whom time points, interventions, and endpoints can be more clearly defined and controlled. There is still controversy as to the optimal timing, route, and composition of nutritional interventions. Less well delineated are outcomes and recommendations for polymorbid hospitalized general medical patients. These patients often are seen with varying degrees of chronic malnutrition exacerbated by acute or chronic medical illness, and they may have coexisting conditions, each presenting challenges to the nutritional and metabolic milieu. As in other clinical settings, malnutrition and ongoing suboptimal food intake have been associated with failure to thrive, higher rates of infection, and greater hospital length of stay, readmission, and mortality, as well as increased health care costs. Well-designed intervention studies with clear outcomes in this population are more challenging, making guidelines difficult to design.

In this issue of JAMA Internal Medicine, Bally and colleagues present an appropriately conducted meta-analysis of trials addressing nutritional intervention in malnourished medical inpatients. They analyzed 22 randomized clinical trials of more than 3700 patients that looked primar-