Original Investigation

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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Invited Commentary

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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] Deleterious 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 ongoing or unpublished trials. We also contacted experts working in the field of malnutrition to identify additional or unpublished 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 resolved 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 associated with individual RCTs.[17] We used the following criteria: (1) random sequence generation (selection bias); (2) randomization concealment (selection bias); (3) blinding (performance bias and detection bias), separated for blinding of participants and personnel, and blinding of outcome assessment; (4) incomplete outcome data (attrition bias); (5) selective reporting (reporting bias); and (6) other bias. Furthermore, 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 intervention characteristics and reported data on efficacy outcomes using a standardized data extraction template. Any disagreements were resolved by discussion or by consulting a third reviewer (P.S.). Continuous outcomes were most often reported as the absolute mean change from baseline, which we used directly to pool data. The absolute mean change was calculated in case continuous data were reported as preintervention and postintervention measures or percentage change. If standard deviations were missing and we did not receive information from study authors, we assumed missing standard deviations to be the mean (SD) of those studies in which this information was reported. We investigated the effect of this assumption 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 complete 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 statistical 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 standard χ^2 test with a significance level of $\alpha = .10$. In view of the low power of this test, we also considered the I^2 statistic, which quantifies inconsistency across studies, to assess the effect of heterogeneity on the meta-analysis.[19] An I^2 statistic of 50% or more indicates a considerable level of heterogeneity.

We used visual inspection of funnel plots to assess publication 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 malnutrition 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

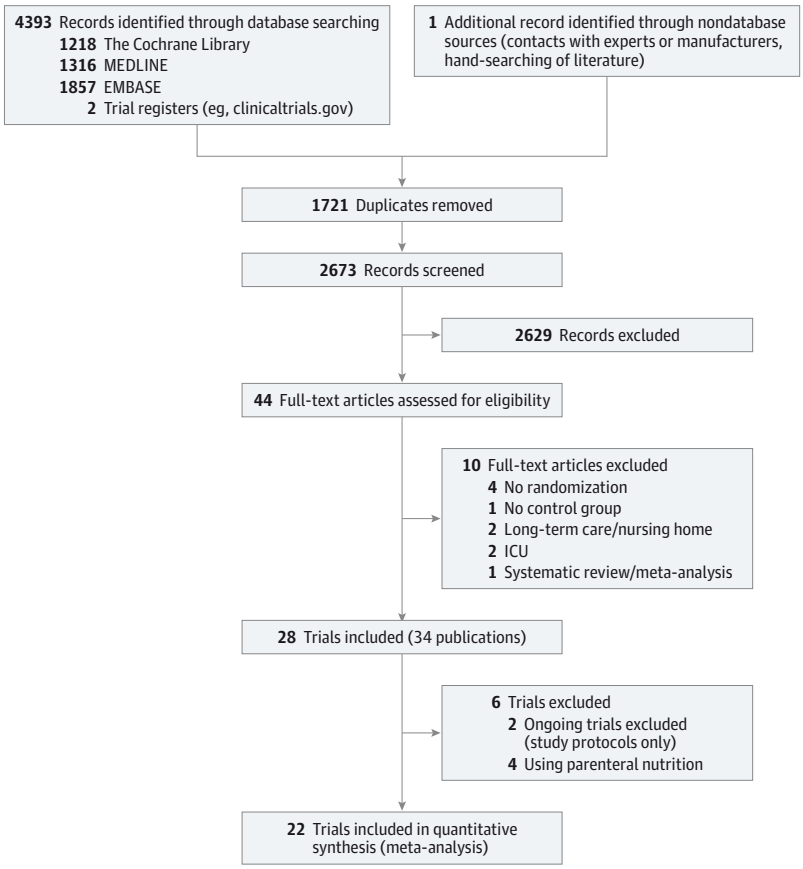
Our systematic search identified 4393 titles and abstracts of potentially eligible studies from electronic databases and one additional record through contact with experts. After removal of duplicates, 2673 records were screened, and 44 full texts were assessed for eligibility. Of these results, 22 RCTs (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 intervention. Additional characteristics of the included RCTs are summarized in **Table 1**.

Risk-of-Bias Assessment

We investigated performance bias, detection bias, and attrition bias separately for objective and subjective outcome measures in each individual trial as recommended by the Cochrane Collaboration (eAppendix in the Supplement). Appropriate random sequence generation and randomization concealment 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 interventions 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 support on mortality was low and was low to very low for all other outcomes.

Figure 1. Study Flow Diagram



ICU indicates intensive care unit.

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 1. Overview of Included Studies

Source	Patient Population	Country	Total Sample Size	Intervention Group	Control Group
Broqvist et al,[21] 1994	Congestive heart failure	Sweden	21	Normal hospital food and between meals, with 500 mL of ONS daily containing 30 g of protein and 750 kcal	Normal hospital food and 1:10 diluted placebo version of ONS
Bunout et al,[22] 1989	Alcoholic liver disease	Chile	36	Oral diet, including 50 kcal/kg/d, 1.5 g of protein per kg daily, casein-based product	Standard diet
Feldblum et al,[23] 2011	Hospitalized adults ≥65 y at nutritional risk	Israel	259	Individual nutritional treatment, 237 mL containing 12.6 g of fat, 13 g of protein, and 47.3 g of carbohydrates (total, 360 kcal), in addition to food fortification	Routine care on request
Gariballa et al,[24] 2006	Hospitalized acutely ill older patients	England	445	2 Bottles (200 mL each) of ONS daily, 995 kcal/d plus vitamins	Oral placebo (60 kcal)
Gazzotti et al,[25] 2003	Patients ≥75 y and at risk for undernutrition	Belgium	80	Standard hospital food and 1 Clinutren soup (Nestlé Health Science), 500 kcal/d, 21 g of protein daily	Standard hospital food, no supplements
Hickson et al,[26] 2004	Acutely ill elderly inpatients	England	592	Nutritional care from health care assistants, snacks and drinks	Usual care
Hogarth et al,[27] 1996	Elderly medical inpatients	England	25	1. Daily 750 mL of oral glucose supplement (540 kcal) and capsules containing vitamins A (8000 U), B_1 (15 mg), B_2 (15 mg), B_3 (50 mg), B_6 (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	1. Nutrasweet (Nutrasweet Company) glucose drink and capsules containing vitamins A (8000 U), B_1 (15 mg), B_2 (15 mg), B_3 (50 mg), B_6 (10 mg), and C (500 mg) during 1 mo 2. Nutrasweet glucose drink and placebo capsules during 1 mo
Holyday et al,[28] 2012	Older patients, depression	Australia	143	Individual modification of hospital meals (fortification), nutritional supplements	Individual modification only on request
McEvoy and James,[29] 1982	Elderly malnourished patients	England	54	2 Sachets of oral Build-up (Lloyds Pharmacy) daily, 36.4 g of protein, 644 kcal	Normal hospital diet
McWhirter and Pennington,[30] 1996	Acutely ill older inpatients	England	86	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	Standard hospital diet
Munk et al,[31] 2014	Hospitalized patients in acute aged care	Denmark	81	Protein-enriched small dishes supplementary to standard food service, ONS, or snacks	Standard hospital diet
Neelemaat et al,[32] 2012	Hospital-admitted malnourished elderly	the Netherlands	210	Energy-enriched and protein-enriched diet, 2 additional servings of an ONS, 2520 kJ/d, 24 g of protein daily, orally 400 U of vitamin D_3, and 500 mg of calcium daily, telephone counseling	Usual care
Ollenschläger et al,[33] 1992	Patients with acute leukemia	Germany	29	Menus of free choice, nutritional education, daily visits by the dietician, record of food intake	Menus of free choice, no nutritional education
Potter et al,[34] 2001 and Roberts et al,[35] 2003	Hospitalized elderly individuals	England	381	120 mL of oral sip-feed supplement 3 times daily, 540 kcal/d, 22.5 g of protein	Normal hospital food
Rüfenacht et al,[36] 2010	Autologous bone marrow transplantation for solid tumors	Switzerland	36	Individual nutritional plan with food enrichment, energy-rich or protein-rich snacks, beverages, energy-dense ONS	2 U of ONS providing 200 mL each with 300 kcal and 12 g of protein
Ryan et al,[37] 2004	Patients at nutritional risk	France	16	Oral supplement (1050 kJ, 250 mL)	Standard hospital breakfast
Saudny-Unterberger et al,[38] 1997	Patients at nutritional risk	Canada	33	ONS 39 kcal/kg/d	Standard food, 29 kcal/kg/d
Somanchi et al,[39] 2011	Malnourished elderly patients	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,[40] 2011	Patients with acute leukemia	Switzerland	132	Individual nutritional care (food supply, fortification of meals with maltodextrins, rapeseed oil, in-between snacks, and ONS), protein intake 1.0 g/kg of body weight	Standard nutritional care, including prescription of ONS on discretion of physician
Vermeeren et al,[41] 2004	Unwell elderly patients	the Netherlands	56	Liquid oral supplement 3 times daily at 125 mL, 2.38 MJ/d, consisting of 20% protein, 20% fat, and 60% carbohydrate	Free choice of normal hospital food and placebo 3 times daily (125 mL, 0 MJ/d)
Vlaming et al,[42] 2001	Older individuals with medical problems	England	549	Normal hospital food plus 400 mL of oral sip-feed supplement, 600 kcal/d, 25.0 g of protein daily, 80.8 g of carbohydrates daily, 19.6 g of fat daily, multivitamins	Normal hospital food plus 400 mL of a placebo, 100 kcal/d, 25 g of carbohydrates daily plus multivitamins
Volkert et al,[43] 1996	Hospitalized undernourished patients	Germany	72	Normal hospital food and 400 mL (2100 kJ) daily of liquid supplement, 200 mL (1050 kJ) daily for the following 6 mo at home	Normal hospital food, usual care without supplements

Abbreviation: ONS, oral nutritional supplement.

Table 2. Outcomes Overall and in Subgroups

Variable	Odds Ratio (95% CI)		Risk Ratio (95% CI)	Mean Difference (95% CI)				
	Mortality	Hospital-Acquired Infections	Nonelective Readmissions	Functional Outcome, Barthel Index Points	Length of Hospital Stay, d	Daily Caloric Intake, kcal	Daily Protein Intake, g	Weight Change, kg
Overall Population								
Intervention group, events/total (%)	133/1361 (9.8)	48/802 (6.0)	10/516 (20.5)	16.7	10.8	1662	54	0.83
Control group, events/total (%)	144/1395 (10.3)	63/812 (7.8)	14/497 (29.6)	16.7	13.0	1314	46	0.19
Overall estimate	0.96 (0.72 to 1.27)	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)	397 (279 to 515)	20.0 (12.5 to 27.1)	0.72 (0.23 to 1.21)
I^2 Test for overall effect, %	49	0	0	85	0	89	91	92
Stratification by Malnutrition								
Established malnutrition	0.70 (0.43 to 1.13)	NA	0.45 (0.20 to 1.02)	4.00 (1.69 to 6.31)	−2.08 (−4.19 to 0.02)	354 (259 to 448)	18.9 (9.7 to 28.2)	1.22 (0.06 to 2.38)
Risk for malnutrition	1.14 (0.83 to 1.57)	0.75 (0.50 to 1.11)	0.73 (0.59 to 0.90)	−0.26 (−0.72 to 0.20)	−0.24 (−0.94 to 0.46)	434 (245 to 624)	17.8 (3.7 to 31.9)	0.80 (0.45 to 1.16)
I^2 Test for subgroup difference, %	64	NA	21	92	49	0	0	0
Stratification by Mortality Risk in Control Group								
High mortality risk, ≥10%	0.77 (0.59 to 1.02)	0.77 (0.17 to 3.46)	NA	0.85 (−1.47 to 3.16)	−0.89 (−2.50 to 0.72)	231 (81 to 380)	16.0 (2.9 to 29.9)	0.41 (−0.42 to 1.24)
Low mortality risk, <10%	1.45 (0.99 to 2.13)	0.75 (0.50 to 1.13)	0.73 (0.59 to 0.90)	−0.30 (−0.86 to 0.26)	−0.15 (−0.91 to 0.61)	455 (321 to 587)	18.9 (11.5 to 26.4)	0.83 (0.47 to 1.19)
I^2 Test for subgroup difference, %	86	0	NA	0	0	79	0	0
Stratification by Adherence to Nutrition Protocol								
High adherence	1.17 (0.69 to 1.99)	0.71 (0.41 to 1.24)	0.66 (0.43 to 1.01)	NA	−0.09 (−0.99 to 0.88)	430 (324 to 537)	20.0 (13.5 to 26.6)	0.90 (0.55 to 1.25)
Low adherence	0.78 (0.53 to 1.13)	0.79 (0.45 to 1.38)	0.72 (0.57 to 0.92)	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)	0.17 (−0.51 to 0.84)
I^2 Test for subgroup difference, %	35	35	0	NA	0	95	67	72
Stratification by Route of Nutritional Therapy								
Oral feeding, noninterventional	0.97 (0.68 to 1.38)	0.75 (0.50 to 1.11)	0.73 (0.59 to 0.90)	0.33 (−0.88 to 1.55)	−0.29 (−0.97 to 0.40)	383 (261 to 505)	17.8 (10.9 to 24.8)	0.72 (0.23 to 1.21)
Enteral feeding	NA	NA	0.45 (0.2 to 1.02)	NA	−2.60 (−5.32 to 0.12)	613 (318 to 908)	48.6 (36.2 to 61.0)	NA
I^2 Test for subgroup difference, %	NA	NA	21	NA	52	50	94	NA

Abbreviation: NA, not applicable.

Body Weight and Nutritional Intake

Sixteen studies reported weight change from the time of randomization to the end of follow-up (until hospital discharge in most studies). Overall, weight increase was significantly higher in intervention group patients compared with control group patients (mean weight increase, 0.72 kg; 95% CI, 0.23-1.21 kg). This finding was true in most trials, although heterogeneity was high. Overall, daily caloric intake was significantly higher in intervention group patients compared with control group patients (difference, 397 kcal; 95% CI, 279-515 kcal). Similarly, daily protein intake was significantly higher in intervention group patients compared with control group patients (difference, 20.0 g/d; 95% CI, 12.5-27.1 g/d).

Sensitivity Analyses

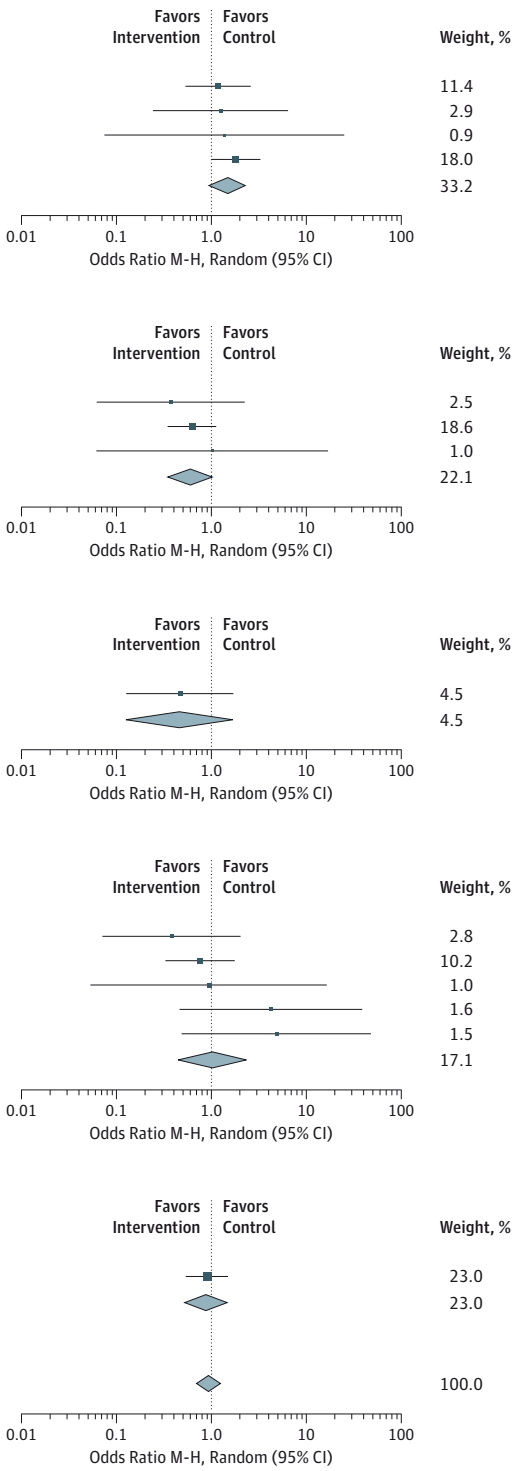
In sensitivity analyses, we stratified trials by degree of malnutrition, control group mortality, adherence to nutrition protocols, and route of nutritional support (oral vs enteral feeding) (eAppendix in the Supplement). There were suggestions of larger benefits from nutritional therapy for the subgroup 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 in-

Figure 2. Forest Plot Comparing Nutritional Intervention vs Control for Mortality

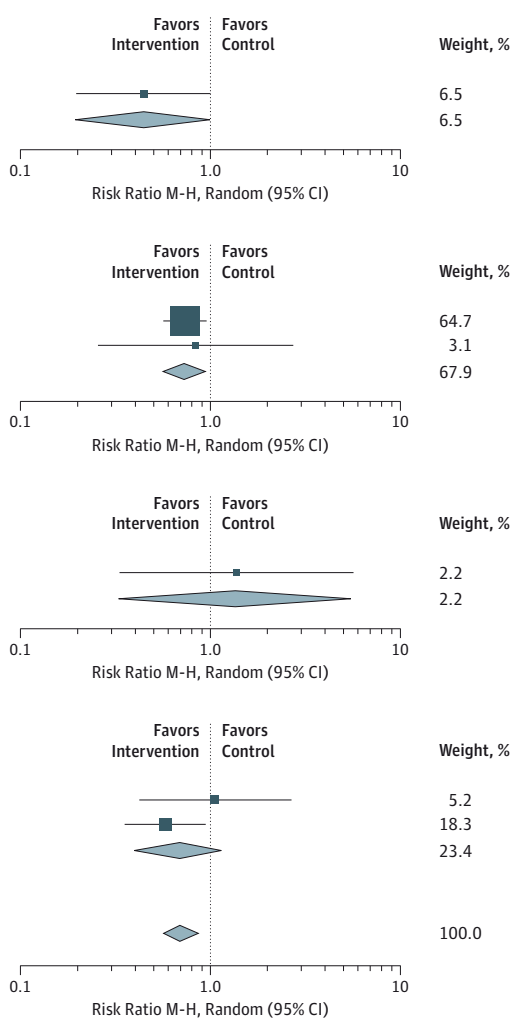
Study or Subgroup	Nutritional Intervention Events	Nutritional Intervention Total	Control Events	Control Total	Odds Ratio M-H, Random (95% CI)	Weight, %
Oral feeding alone vs placebo						
Vlaming et al,[42] 2001	14	274	12	275	1.18 (0.54-2.60)	11.4
Hogarth et al,[27] 1996	5	9	8	16	1.25 (0.24-6.44)	2.9
Broqvist et al,[21] 1994	1	9	1	12	1.38 (0.07-25.43)	0.9
Gariballa et al,[24] 2006	32	222	19	223	1.81 (0.99-3.30)	18.0
Subtotal (95% CI)	52	514	40	526	1.52 (0.96-2.39)	33.2
Heterogeneity: $\tau^2=0.00$; $\chi^2_3=0.77$ ($P=.86$); $I^2=0\%$						
Test for overall effect: $z=1.80$ ($P=.07$)						
Oral feeding alone vs usual care						
Bunout et al,[22] 1989	2	17	5	19	0.37 (0.06-2.25)	2.5
Potter et al,[34] 2001	21	186	33	195	0.62 (0.35-1.13)	18.6
Munk et al,[31] 2014	1	40	1	41	1.03 (0.06-16.98)	1.0
Subtotal (95% CI)	24	243	39	255	0.61 (0.35-1.05)	22.1
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=0.43$ ($P=.81$); $I^2=0\%$						
Test for overall effect: $z=1.79$ ($P=.07$)						
Oral feeding alone vs no support						
Volkert et al,[43] 1996	4	35	8	37	0.47 (0.13-1.72)	4.5
Subtotal (95% CI)	4	35	8	37	0.47 (0.13-1.72)	4.5
Heterogeneity: not applicable						
Test for overall effect: $z=1.14$ ($P=.25$)						
Oral feeding with dietary advice vs usual care						
Starke et al,[40] 2011	2	66	5	66	0.38 (0.07-2.04)	2.8
Neelemaat et al,[32] 2012	11	105	14	105	0.76 (0.33-1.76)	10.2
Saudny-Unterberger et al,[38] 1997	1	17	1	16	0.94 (0.05-16.37)	1.0
Holyday et al,[28] 2012	4	71	1	72	4.24 (0.46-38.90)	1.6
Rüfenacht et al,[36] 2010	4	18	1	18	4.86 (0.49-48.57)	1.5
Subtotal (95% CI)	22	277	22	277	1.05 (0.44-2.46)	17.1
Heterogeneity: $\tau^2=0.22$; $\chi^2_4=5.12$ ($P=.28$); $I^2=22\%$						
Test for overall effect: $z=0.10$ ($P=.92$)						
Oral feeding with dietary advice vs no support						
Hickson et al,[26] 2004	31	292	35	300	0.90 (0.54-1.50)	23.0
Subtotal (95% CI)	31	292	35	300	0.90 (0.54-1.50)	23.0
Heterogeneity: not applicable						
Test for overall effect: $z=0.41$ ($P=.68$)						
Total (95% CI)	133	1361	144	1395	0.96 (0.72-1.27)	100.0
Heterogeneity: $\tau^2=0.02$; $\chi^2_{13}=14.12$ ($P=.37$); $I^2=8\%$						
Test for overall effect: $z=0.30$ ($P=.76$)						
Test for subgroup difference: $\chi^2_4=7.86$ ($P=.10$); $I^2=49\%$						



M-H indicates Mantel-Haenszel.

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-

Figure 3. Forest Plot Comparing Nutritional Intervention vs Control for Nonelective Readmissions



M-H indicates Mantel-Haenszel.

[a] Calculated and approximated from readmission rate.

[b] Calculated and approximated from readmission frequency.

tional 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 intervention group patients, suggesting that improved nutritional status might positively affect the recurrence of illnesses in medical patients after hospital discharge. The number needed to treat for readmission was 23 (95% CI, 16-52), assuming a readmission proportion of 15%.[44] Also, in the subgroup 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)[45-56] 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 demon-

strated in the critical care patient population,[4] 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[11,12] 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.[8,57,58] During the acute phase of illness, the body mobilizes substrates from muscle and fat tissue to match increases in resting energy expenditure.[59] 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.[3] However, other research demonstrated benefits from individually optimized energy supplementation with early parenteral feeding (3 days after admission) in severely ill patients in the intensive care unit for whom enteral nutrition alone was insufficient.[60] The contradictory findings from these critical care trials may be partly explained by the differences in time points when feeding was initiated. Our analysis found no evidence of harm associated with nutritional therapy in medical inpatients, 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 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,[18] 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.[6]

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 nonelective admissions and a suggestion of shorter length of hospital stay. High-quality RCTs are needed to provide more definite conclusions.

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Invited Commentary

Nutritional Support on the Medical Wards—Thought for Food

Jonathan P. Kushner, MD; Joseph A. Lacy, RD; Steven R Gay, MD

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,[1] 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[2] that the issue of nutrition of inpatients was frequently neglected. Well before that, suboptimal nutrition states were closely associated with poor outcomes.[3] However, 40 years after our eyes were opened to this long-ignored issue, we struggle to identify appropriate patients and efficacious nutritional interventions.

Related article

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.[4] 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 end points 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[5] 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 primarily at polymorbid medical inpatients between 1989 and 2014. High heterogeneity across the studies was seen, as well as some unknown biases. As expected, nutritional intervention groups (mostly oral supplements or counseling, with fewer receiving enteral tube feeding) had greater intake and weight gain than control arms, but the primary outcome of mortality and important secondary outcomes of infections, physical function, or hospital length of stay were not aided by nutritional intervention. There was a trend to a shorter length of stay in a subgroup of already malnourished patients. Nonelective readmissions in the intervention groups were statistically less, with a number needed to treat of 23. Overall, even with the potential for publication and attrition bias, the benefits of nutritional intervention in this population appear to be modest. However, while the hospital readmission rate was not the primary outcome of this meta-analysis, the improvement seen presents a potentially important piece of evidence to support nutritional intervention in light of rising health care costs in the 21st century. To date, there have been limited cost-effective analyses of nutritional intervention in medical inpatients,[6] perhaps a topic in need of further investigation.

Earlier, Potter et al[7] examined 30 randomized trials of routine oral or enteral protein supplementation in a meta-analysis of more than 2000 adults. They found improved nutritional indexes but an uncertain trend to reduced mortality, hampered by publication bias and trial methods. The population was composed of both healthy elderly outpatients and a mix of surgical and medical inpatients using predominantly oral supplementation. Subgroup analysis showed a less impressive mortality benefit for supplementation in medical patients. The large Cochrane Collaboration meta-analysis by Milne et al[8] examined oral nutritional supplementation in more than 10 000 elderly patients in 62 trials. The majority were hospitalized patients. Again, nutritional status improved with intervention, but other beneficial outcomes were not demonstrated because of problems with study methods and quality. Reduced mortality in the already malnourished subgroup was suggested. Inadequate duration of supplementation was cited as a potential drawback. A large systematic review of randomized trials of oral or tube-fed supplementation by Koretz et al[9] found benefits with oral supplementation only in the already malnourished elderly among medical patients.

Joint Commission on Accreditation of Healthcare Organizations regulations have prompted more rigorous nutritional screening in hospitalized patients.[10] In turn, a number of organizations have promulgated pathways and guidelines not only for screening and assessment of all hospitalized patients but also for nutritional intervention. However, the recommendations outside of the critical care or perioperative arena in many cases are based on low levels of evidence, derived from trials that fail to provide clear-cut evidence of beneficial and cost-effective nutritional intervention.

Several challenges remain. Our present-day practices may result in mishandling the delicate balance of nutritional, metabolic, and immune system function, to our patients' detriment. Current composition and timing of nutritional therapy may be suboptimal. Oral supplements and some tube feedings contain significant amounts of sugar, corn syrup solids, and maltodextrin, which may affect glycemic index and other responses. Continuous tube feeding and parenteral nutrition may potentially desynchronize a range of anabolic metabolic processes. The relationships among nutrition, activity, and physical therapy to optimize nutrient and growth effect may be underappreciated.

Medical inpatients represent a diverse group with complicated needs, and it may not be possible to make broad recommendations across this population. We should continue to strive for high-quality randomized studies that more clearly delineate appropriate target populations for nutritional intervention and, with that, the specific route, type, and amount of nutrition that results in the best outcome. Even for the less invasive and less expensive option of dietary counseling and oral supplements, we must be sure that these methods also avoid unwanted negative effects and meet cost-effective standards. The exciting challenge of defining optimal nutritional interventions for specific situations continues.

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