Annals of Internal Medicine | Review

Meta-Analysis: Protein and Energy Supplementation in Older People

Anne C. Milne, MSc; Alison Avenell, MD; and Jan Potter, MBChB

Background: Protein and energy undernutrition is common in older people, and further deterioration may occur during illness.

Purpose: To assess whether oral protein and energy supplementation improves clinical and nutritional outcomes for older people in the hospital, in an institution, or in the community.

Data Sources: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, HealthStar, CINAHL, BIOSIS, and CAB abstracts. The authors included English- and non–English-language studies and hand-searched journals, contacted manufacturers, and sought information from trialists. The date of the most recent search of CENTRAL and MEDLINE is June 2005.

Study Selection: Randomized and quasi-randomized controlled trials of oral protein and energy supplementation compared with placebo or control treatment in older people.

Data Extraction: Two reviewers independently assessed trials for inclusion, extracted data, and assessed trial quality. Differences were resolved by consensus.

Data Synthesis: Fifty-five trials were included (n = 9187 randomly assigned participants). For patients in short-term care hospitals who were given oral supplements, evidence suggested fewer complications (Peto odds ratio, 0.72 [95% CI, 0.53 to 0.97]) and reduced mortality (Peto odds ratio, 0.66 [CI, 0.49 to 0.90]) for those undernourished at baseline. Few studies reported evidence that suggested any change in mortality, morbidity, or function for those given supplements at home. Ten trials reported gastrointestinal disturbances, such as nausea, vomiting, and diarrhea, with oral supplements.

Limitations: The quality of most studies, as reported, was poor, particularly for concealment of allocation and blinding of outcome assessors. Many studies were too small or the follow-up time was too short to detect a statistically significant change in clinical outcome. The clinical results are dominated by 1 very large recent trial in patients with stroke. Although this was a high-quality trial, few participants were undernourished at baseline.

Conclusions: Oral nutritional supplements can improve nutritional status and seem to reduce mortality and complications for undernourished elderly patients in the hospital. Current evidence does not support routine supplementation for older people at home or for well-nourished older patients in any setting.

Ann Intern Med. 2006;144:37-48. www.annals.org
For author affiliations, see end of text.

Undernutrition among older people is a continuing source of concern (1, 2). Older people have longer periods of illness and longer hospital stays (3), and data show that up to 55% of elderly hospitalized patients are undernourished at admission (4, 5). Malnutrition is associated with poorer recovery in a broad range of patients and conditions (6–8). However, poor nutritional status may be a marker for severity of existing medical conditions, and whether improving nutritional status with oral protein and energy supplementation can improve acute or chronic medical conditions is not clear.

Recent systematic reviews examining the potential benefits of nutritional supplementation in older people include Stratton and colleagues' review (9) of randomized and nonrandomized trials (166 trials; 7630 patients) across all disease groups and settings, which concluded that nutritional supplementation had positive effects on nutritional outcomes and mortality in elderly people and, in some cases, clinical and functional benefits. Potter's meta-analysis (10) of 18 trials that included older patients both in the hospital and in the community suggested a statistically significantly lower mortality for the supplemented group (odds ratio, 0.61 [95% CI, 0.45 to 0.82]). A recent update of a Cochrane review by Avenell and Handoll (11) of nutritional supplementation for hip fracture care in older people found some evidence that oral protein and energy feeds (evaluated by 8 trials) reduced unfavorable outcome (death or complications) but did not observe a demonstrable effect on deaths alone. Overall, the evidence was weak because of methodologic defects in the reviewed studies. Oral nutritional supplements are widely prescribed for older people both in the hospital and in the community. We undertook a systematic review of randomized trials of oral protein and energy supplementation to assess clinical and nutritional outcomes for older people who are offered supplements in different settings.

Methods

We identified studies and performed the analyses according to the Cochrane method (12). The search included the following databases: Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 2, 2005), MEDLINE (1966 to June 2005), EMBASE (1980 to March 2004), HealthStar (1975 to March 2001), CI-

See also:

Print
Editors' Notes 38
Editorial comment. 59

Web-Only
Appendix Tables
Appendix Figures
CME quiz
Conversion of figures and table into slides

Context

Physicians sometimes recommend nutritional supplementation for sick, older persons.

Contribution

This review summarizes 55 trials of protein and energy supplementation in people older than 65 years of age. Compared with placebo or no supplementation, nutritional supplements did not affect morbidity or mortality in people living in the community. Among older and undernourished hospitalized patients, supplements sometimes reduced mortality and complications, such as infections, poor wound healing, and pressure sores. Oral supplements also sometimes caused nausea, vomiting, and diarrhea.

Cautions

Many trials were small or had short follow-up times and used outcome assessors who knew which patients took supplements.

—The Editors

NAHL (1982 to March 2004), BIOSIS (1985 to March 2004), and CAB abstracts (1973 to March 2004). We included English- and non–English-language studies. We also hand-searched nutrition journals and reference lists and contacted oral nutritional supplement manufacturers.

We included randomized or quasi-randomized trials with an minimum intervention of 1 week. Groups of study participants had to have a minimum average age of 65 years. We included all patient groups, with the exception of people in critical care or those who were recovering from cancer treatment. We included commercial supplements, other milk-based supplements, and fortification of normal food sources. We excluded studies of specially designed immunomodulatory supplements or supplements of specific amino acids. The full description of the search strategy is available elsewhere (13). We contacted trialists for further information on ambiguous numerical data and to allow trial quality to be more accurately assessed.

We examined the following outcomes as prespecified in our protocol: all-cause mortality, number of people with morbidity or complications, length of hospital stay, functional status, participants' perceived quality of life, percentage change in weight, percentage change in mid-arm muscle circumference, acceptance of the supplement, and adverse effects. We included trials that reported at least 1 relevant clinical outcome measure. Two reviewers independently extracted outcome data from the included trials and performed quality assessment of trials. We used a 10-item quality assessment checklist, which is based on the quality assessment tool of the Cochrane Bone, Joint and Muscle Trauma Group (14), to rate studies between 0 and 2 points for each item, including assessment of allocation concealment, intention-to-treat analysis, and blinding of outcome assessors. We resolved all differences by discussion.

Statistical Analysis

We combined data for the meta-analysis for the dichotomous variables of mortality and complications and adverse effects by using RevMan 4.2 software (Cochrane Collaboration, Oxford, United Kingdom). Low event rates pose particular problems for summarizing data in a systematic review. Default use of a correction for continuity or simply adding 0.05 to each cell when counts are less than 5.00 tends to produce biased estimates. Many methods are recommended in the literature (15). The widely available Peto method (16) produces estimates without the need for 0-cell corrections, and it produces unbiased estimates when equal numbers of patients are in each group (17). For each study, we calculated Peto odds ratios and combined the results by using fixed-effects models with 95% confidence limits. We calculated weighted mean difference and 95% CIs for length of hospital stay, percentage weight change, and percentage mid-arm muscle circumference change by using a fixed-effects model. We explored heterogeneity between comparable trials with the I^2 test (18) by using greater than 50% as the cutoff value for statistically significant heterogeneity. When evidence suggested heterogeneity, we applied a random-effects model.

The trials reported body weight and anthropometric measures in several ways. For meta-analyses of weight change and mid-arm muscle circumference change, we selected the mean and SD of the percentage weight change during the trial period because of their clinical relevance (19). When the percentage weight change was not available, we calculated the difference between the initial and final body weight, expressed as a percentage of baseline weight and an SD of 10% inferred. This SD was conservative and was at the upper limit of any observed result. If baseline weight was not reported, we assumed a standard value of 60 kg. As in Potter and colleagues' study (19), we chose mid-arm muscle circumference as the anthropometry measure because it is a measure of muscle. When this was not described in the trial, we derived it from the mid-arm circumference or mid–upper arm circumference and triceps skinfold by using a standard formula (20).

We performed prespecified subgroup analyses of the mortality data by comparing 1) baseline nutritional status as defined by the investigators (nourished or undernourished), 2) mean age (<75 years or ≥75 years), 3) amount of kilojoules provided in the supplement (<1674 kJ [<400 kcal] or ≥1674 kJ [≥400 kcal]), 4) duration of intervention (<35 days or ≥35 days), and 5) patient health (well or unwell).

We performed an exploratory subgroup analysis for mortality on the basis of diagnostic group (hip fracture, chest conditions, stroke, and congestive heart failure), geriatric conditions (trials that included frail patients with a variety of conditions), and perioperative surgical patients. We also stratified the trials by setting (short-term care hospital, long-term care institutions [including nursing homes], and home in the community) because we sus-

pected differences in the nature and duration of the intervention in different settings. Prespecified sensitivity analysis included only trials that reported clearly concealed randomization. We evaluated the potential for publication bias by using a funnel plot. In addition, we performed a sensitivity analysis to address possible heterogeneity between findings of small and large trials, the latter having more than 100 participants in each group.

Role of the Funding Sources

The Medical Research Council, United Kingdom; Chief Scientist Office of the Scottish Executive Health Department, United Kingdom; and the Student Awards Agency for Scotland, United Kingdom, funded the study. The funding sources had no role in the design, conduct, or reporting of the study or in the decision to submit the paper for publication.

RESULTS

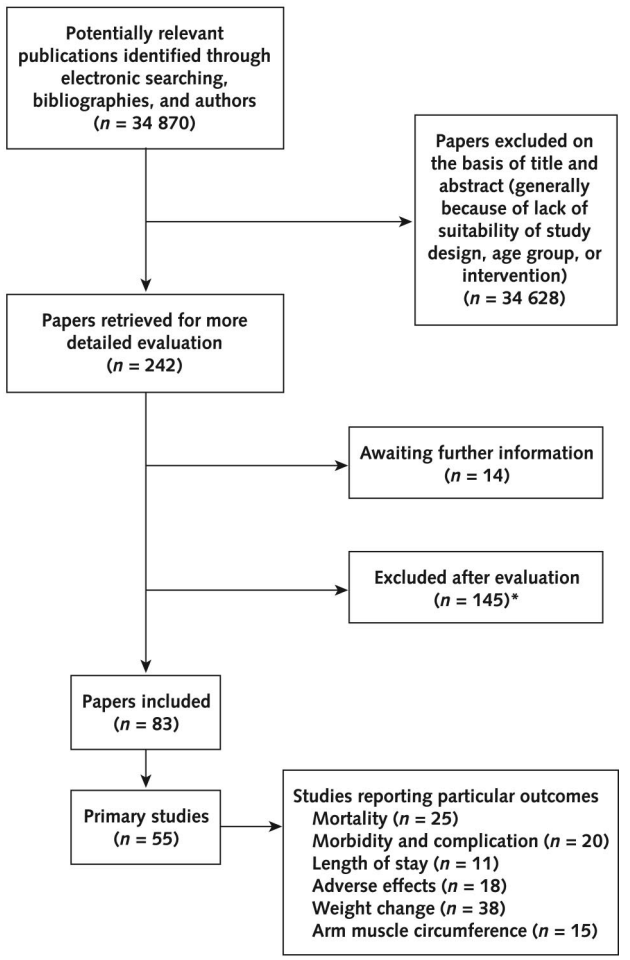
Description of Studies

From more than 34 000 titles or abstracts screened, we included 55 studies in our review (**Figure 1**). The 55 studies (21–75) recruited 9187 participants (**Appendix Tables 1** and **2**, available at www.annals.org). Nearly half of the participants were from the recent Feed Or Ordinary Diet (FOOD) trial (37) of oral nutritional supplements for patients with stroke. Most trial participants (74%; 25 trials) were hospitalized inpatients. Fewer patients were at home in the community (16%; 21 trials) or in long-stay, elderly care, or continuing care wards or nursing homes (10%; 9 trials). Overall, most participants were patients with stroke (45%; 2 trials) or were mixed groups with various geriatric conditions (42%; 33 trials). We also included trials of patients with hip fracture (7%; 10 trials), patients with chronic obstructive pulmonary disease (5%; 7 trials), surgical patients (1%; 2 trials), and patients with congestive heart failure (<1%; 1 trial).

The source of funding was unclear for most studies. Eleven trials were coauthored by an employee of the manufacturer of the oral supplement or were fully funded by the manufacturer (**Appendix Table 1**, available at www.annals.org). The interventions in the trials aimed to provide between 175 kcal (732 kJ) and 1000 kcal (4.2 MJ) and between 10 g and 63 g of protein daily. Fifteen trials provided less than 1674 kJ (400 kcal) per day, 30 trials provided 1674 kJ or more (≥400 kcal) per day, and 10 trials did not specify the supplemented energy value. Most supplements included vitamins and minerals. The intervention period ranged from 10 days to 18 months and was 35 days or more in 33 trials, was less than 35 days in 12 trials, and was unspecified in 10 trials. Eight studies, including the FOOD trial (37), provided supplements until hospital discharge (estimated mean ranging from 12 days to 38 days). The duration of follow-up was usually the same as that of the intervention.

Seventeen trials, including the FOOD trial (37), reported that supplements were well-accepted by most patients, although this was often not defined or was variously defined. Other studies, particularly those offering supplements over longer periods of time, reported major problems with adherence for 24% to 45% of participants (24, 41, 62, 71, 59). Total energy and protein intake were, however, substantially greater than nonsupplemented intake in nearly all studies, although Fiatarone and colleagues (36) highlighted that the increase in intake from the supplements may be partially offset by a reduction in normal food intake. When reported, completeness of follow-up varied between 100% and 27% of those randomly assigned. Participant withdrawal or dropout was 25% or higher in 12 of the 55 trials.

Figure 1. **Flow chart for study selection.**



*Main reasons were study not randomized, intervention did not meet inclusion criteria (nasogastric feeding, high-protein vs. low-protein, early vs. late introduction of feeding, and immunomodulatory supplements), or participants did not fit the inclusion criteria (too young and patients with cancer).

Methodologic Quality of Included Studies

Full details of the quality assessment are available in the Cochrane review (13). **Appendix Table 2** (available at www.annals.org) presents total scores. The trials had low scores, with only 27 of 55 trials achieving 50% or more of the maximum quality score. Sixteen studies confirmed adequate concealment of allocation, and 22 studies reported intention-to-treat analysis or we could perform intention-to-treat analysis. The quality was poorest with regard to blinding. Only 9 studies clearly reported the blinding of outcome assessors.

Outcomes

We suspected heterogeneity because of the differences in the nature and duration of the intervention in different settings. We therefore grouped trials post hoc for analysis by setting (that is, short-term care hospital, long-term care institutions [including nursing homes], and community-dwelling elders). The duration of the intervention was 8 weeks or more in 20%, 55%, and 81% of trials set in the hospital, in long-term care, and in the community, respectively. Three hospital-based interventions continued at home after discharge.

Mortality

At the time of last follow-up, which was usually when supplementation was discontinued, nutritional supplementation was associated with reduced mortality from a global analysis of 25 trials (6852 randomly assigned participants), which was borderline statistically significant (Peto odds ratio, 0.86 [CI, 0.74 to 1.00]) (**Figure 2**). For patients in short-term care hospitals, mortality was not statistically significantly reduced (Peto odds ratio, 0.88 [CI, 0.74 to 1.04]), unless only undernourished patients were included (Peto odds ratio, 0.66 [CI, 0.49 to 0.90]) (**Figure 3**). A reduction in mortality from the analysis of patients in long-term care was also not statistically significant (Peto odds ratio, 0.65 [CI, 0.41 to 1.02]). For participants in long-term care, trials were too small and were too few in number to examine the effect of supplementation in nourished and undernourished older people. Evidence did not suggest a reduction in mortality for people living at home regardless of nutritional status (Peto odds ratio, 1.05 [CI, 0.57 to 1.95]). We found no statistically significant heterogeneity within any setting (I^2 = 0% to 12.6%).

Results of the subgroup analysis suggested improved survival with supplementation in undernourished people (17 trials; 2093 participants; 3 trials providing separate results for nourished and undernourished patients) (Peto odds ratio, 0.73 [CI, 0.56 to 0.94]), when people were 75 years of age or older (18 trials; 1611 participants) (Peto odds ratio, 0.64 [CI, 0.49 to 0.85]), when people were offered 1674 kJ or more per day in the supplement (15 trials; 6157 participants) (Peto odds ratio, 0.85 [CI, 0.73 to 0.99]), and when participants were not well (22 trials; 6630 participants) (Peto odds ratio, 0.86 [CI, 0.74 to 1.00]). The I^2 test for heterogeneity was less than 2% for all subgroups.

The results for mortality were statistically significant when we included only trials with clearly concealed randomization (12 trials; 5991 participants) (Peto odds ratio, 0.84 [CI, 0.72 to 0.98]). **Appendix Figure 1** (available at www.annals.org) and our sensitivity analysis do not suggest that small, positive trials were over-represented (21 trials; 1464 participants) (Peto odds ratio, 0.87 [CI, 0.59 to 1.29]) compared with larger trials (4 trials; 5388 participants) (Peto odds ratio, 0.86 [CI, 0.73 to 1.01]). Our post hoc subgroup analyses for mortality based on diagnostic group found statistically significant results for trials that included patients with various geriatric conditions (15 trials; 2313 participants) (Peto odds ratio, 0.69 [CI, 0.52 to 0.92]). No evidence suggested a change in survival with oral supplements from trials of patients with stroke (2 trials; 4063 participants) (Peto odds ratio, 0.92 [CI, 0.76 to 1.11]) or hip fracture (5 trials; 269 participants) (Peto odds ratio, 0.88 [CI, 0.41 to 1.89]). The data were too limited to undertake meta-analyses for other diagnostic groups.

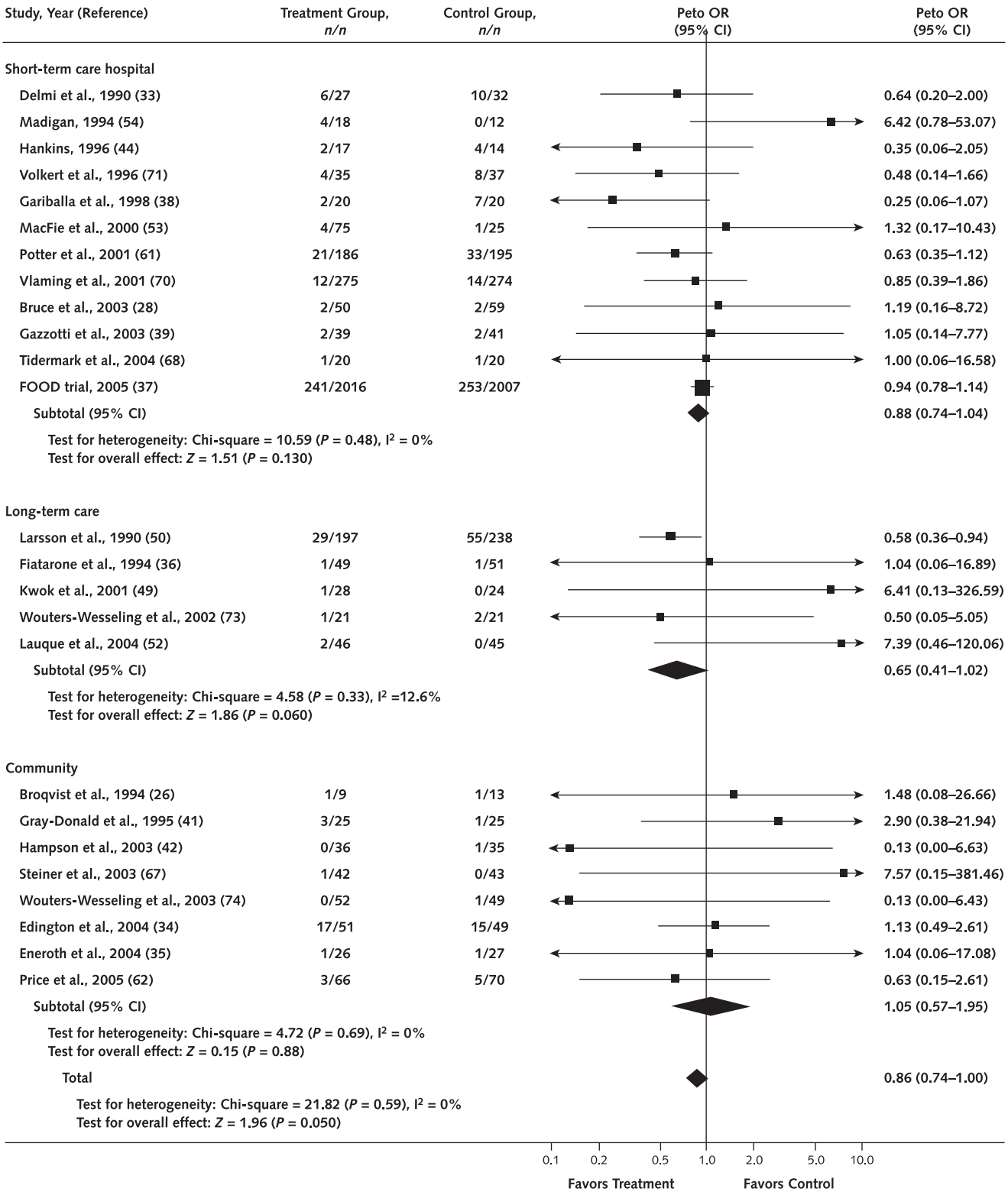
Morbidity and Complications

Twenty trials provided data on morbidity and complications (**Appendix Table 2**, available at www.annals.org). Global meta-analysis of 19 trials (5508 participants) reporting participants with infective complications (38, 61, 62); incomplete wound healing (30, 35); total pressure sores (37, 50); total complications, excluding deaths (26, 33, 44, 53, 68); illness that led to discontinuation (42, 54, 63, 74); exacerbation of chronic obstructive pulmonary disease (67, 69); and hospitalization (52) suggested fewer complications, although this was not statistically significant (Peto odds ratio, 0.82 [CI, 0.65 to 1.03]). Hospitalized patients who were given supplements had a statistically significant decrease in complications (Peto odds ratio, 0.72 [CI, 0.53 to 0.97]). Supplementation did not have a statistically significant effect on morbidity or complications in people in long-term care (Peto odds ratio, 0.92 [CI, 0.56 to 1.52]) or at home (Peto odds ratio, 1.01 [CI, 0.63 to 1.64]) (**Figure 4**). Subgroup analyses based on diagnostic group suggested a reduced risk for complications with supplementation only for patients with hip fracture (4 trials; 147 participants) (Peto odds ratio, 0.48 [CI, 0.24 to 0.96]). In most cases, including the FOOD trial (37), outcome assessors for complications were not blinded to treatment allocation.

Adverse Effects

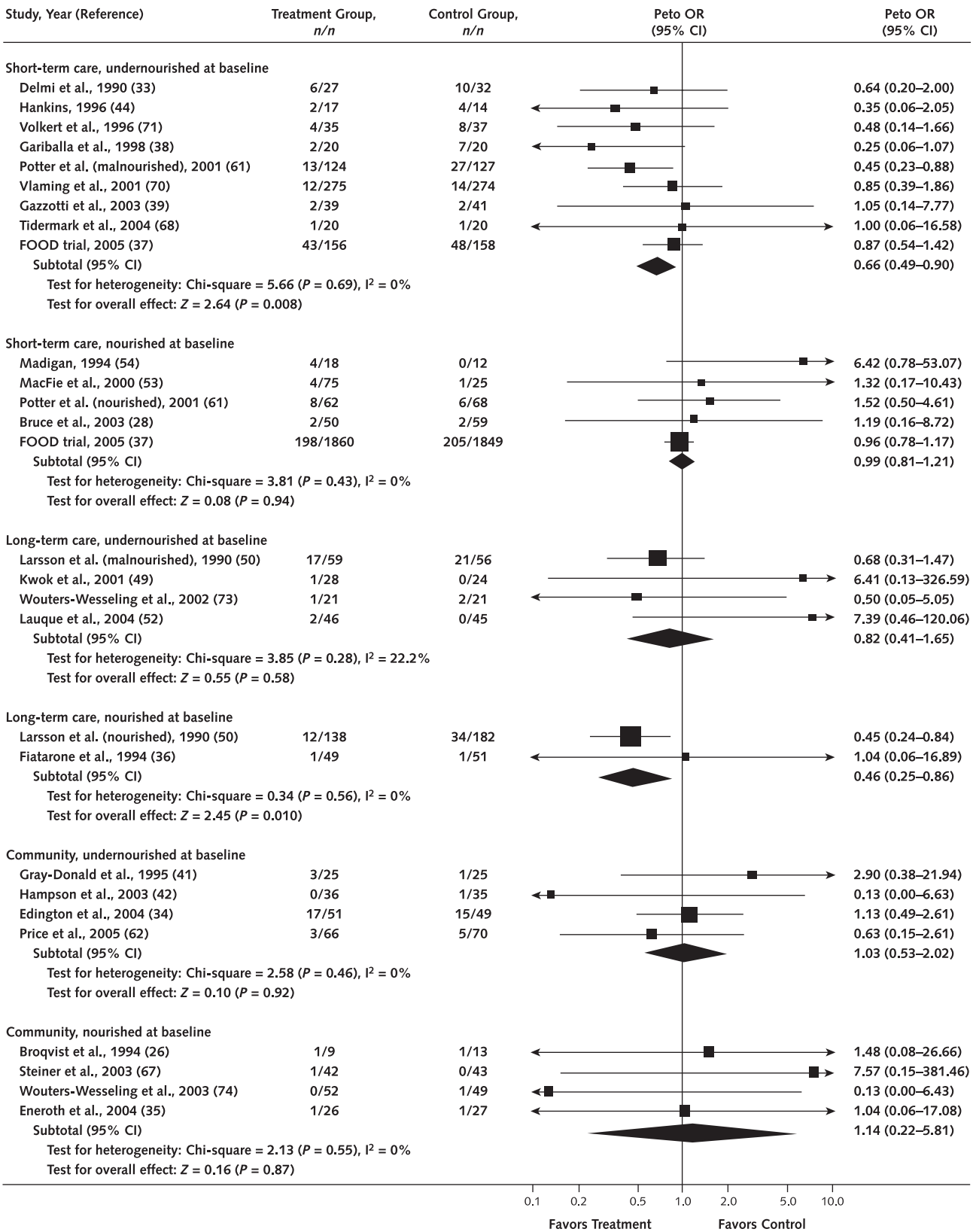
Most trials did not report adequate methods for assessing potential adverse effects. In most trials that discussed adverse effects with supplements (18 trials), no comparison with the control group was performed. Of these trials, 10 reported some problems with tolerance and side effects and 8 reported no adverse effects (**Appendix Table 2**, available at www.annals.org). Meta-analysis of 6 trials (477 participants) that reported participants with adverse effects in both groups suggested a statistically significant effect on gastrointestinal disturbances,

Figure 2. **Meta-analysis of mortality.**



FOOD = Feed Or Ordinary Diet; OR = odds ratio.

Figure 3. **Analysis of mortality data by nutritional status.**



FOOD = Feed Or Ordinary Diet; OR = odds ratio.

such as nausea, vomiting, and diarrhea, with supplements (Peto odds ratio, 3.19 [CI, 1.83 to 5.56]).

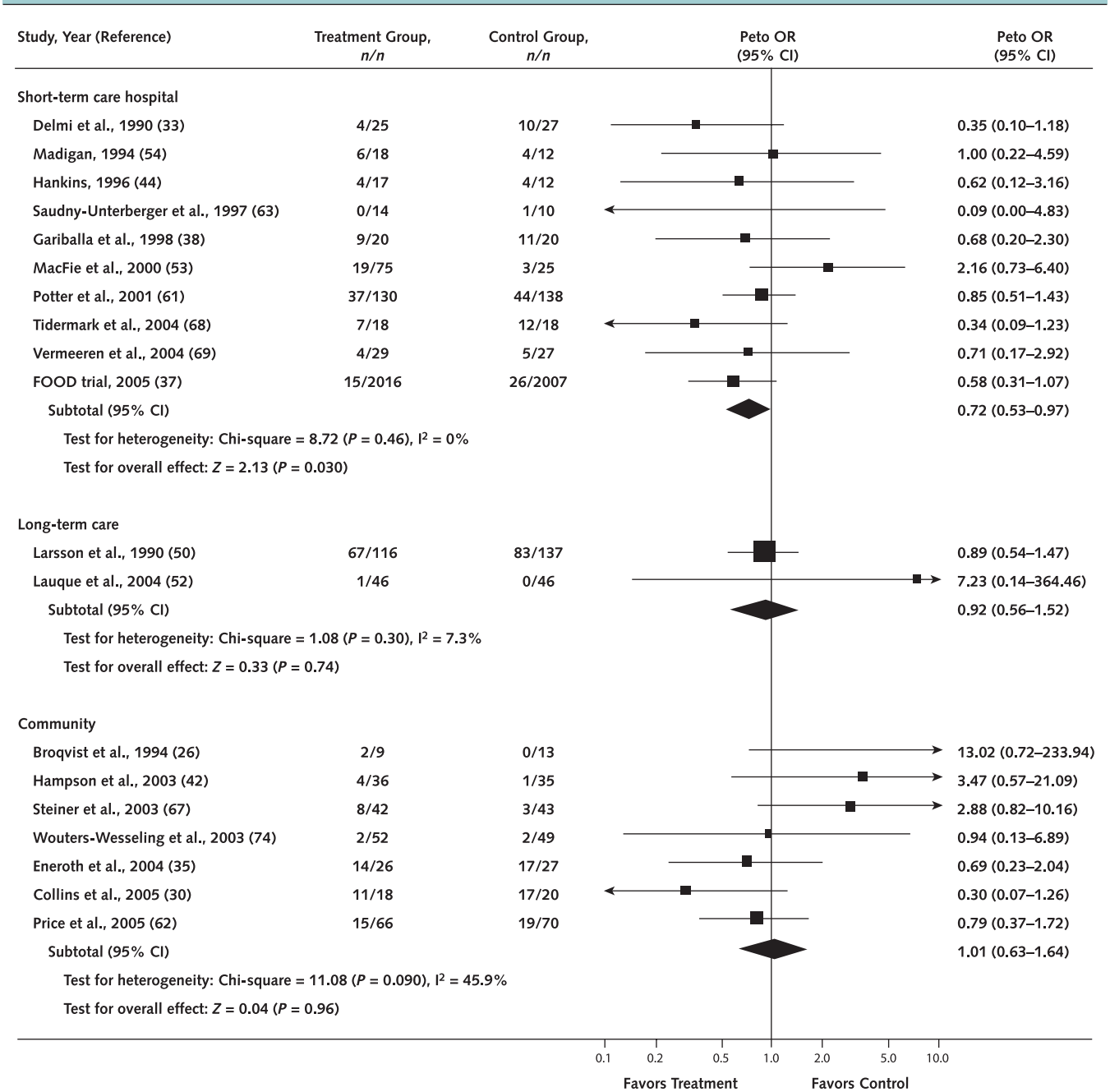
Length of Stay

We combined data on length of hospital stay from 11 studies and stratified them by nutritional status (**Appendix Figure 2**, available at www.annals.org). The trials were heterogeneous (I^2 = 51.6%), and a random-effects model showed no statistically significant effect on length of stay overall (weighted mean difference, −1.17 days [CI, −3.90 days to 1.57 days]). This was not affected by nutritional status, although we observed a trend toward a shorter length of stay for supplemented patients who were undernourished (−3.30 days vs. −0.84 day).

Functional Status and Quality of Life

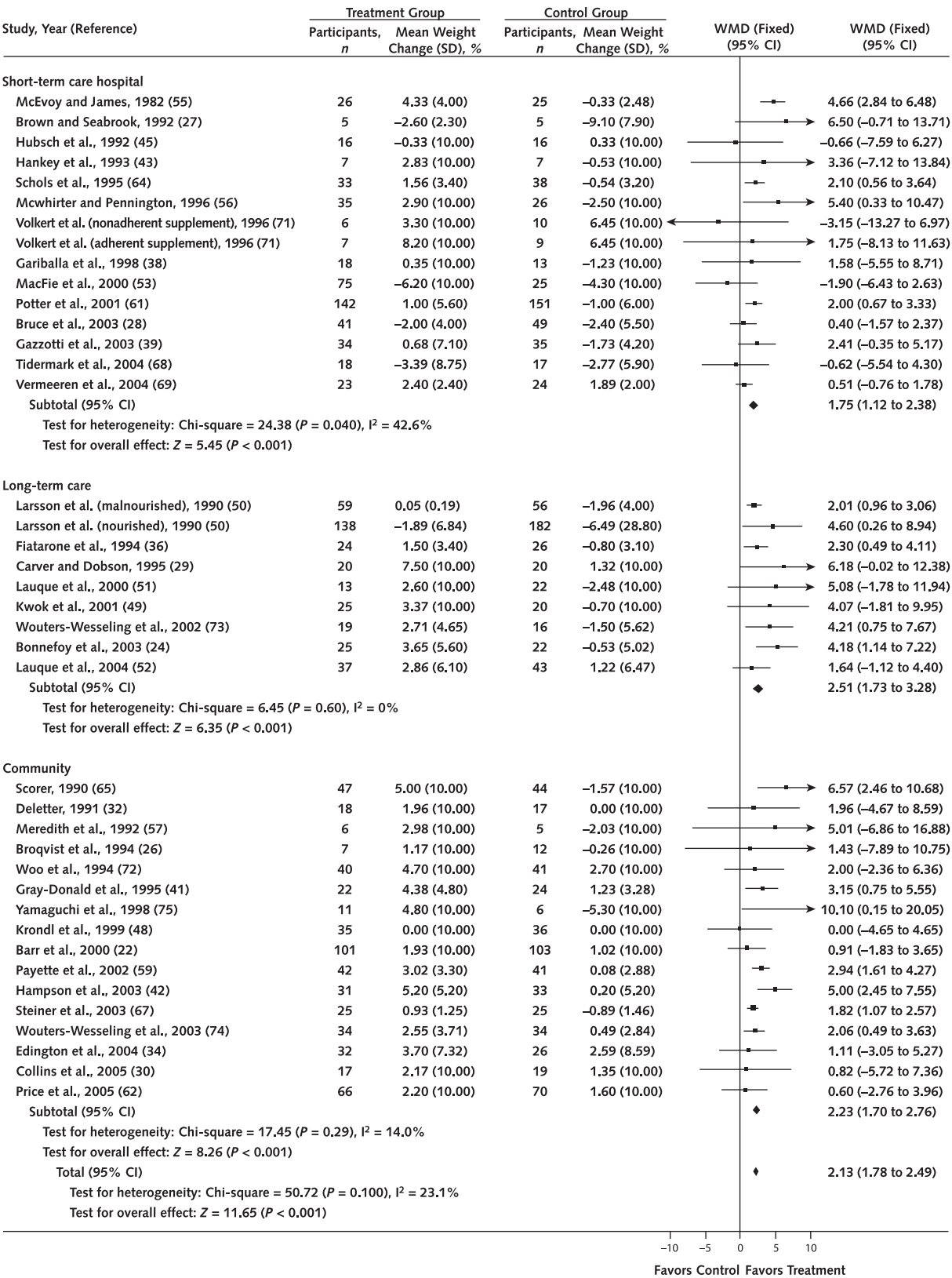
Functional status measures were diverse, and few studies suggested any statistically significant change in func-

Figure 4. **Analysis of participants developing complications.**



FOOD = Feed Or Ordinary Diet; OR = odds ratio.

Figure 5. **Meta-analysis of percentage weight change.**



WMD = weighted mean difference.

tion. Ten studies measured activities of daily living. Only Woo and colleagues (72) found a statistically significant difference between groups at the end of follow-up, 3 months after a chest infection. Eleven studies measured handgrip strength. Only 1 study (62) found a statistically significant improvement between groups with supplementation. The results combined for meta-analysis from 5 trials (282 participants) (59, 62, 67,68, 74) showed no statistically significant effect (standardized mean difference, 0.02 unit [CI, −0.18 unit to 0.22 unit]). Fifteen studies ascertained health-related quality of life by using a variety of measures (for example, Short-Form 36, Euroqol-5D, or Nottingham Health Profile). Only 2 studies reported statistically significant improvements from supplementation between groups at the end of follow-up (34, 42).

Weight Change

In data from 14 trials, the pooled weighted mean difference for percentage weight change in hospitalized patients showed an increase with supplementation of 1.75% (CI, 1.12% to 2.30%) (**Figure 5**). Percentage weight change was 2.51% (CI, 1.73% to 3.20%) for patients in long-term care (8 trials) and 2.25% (CI, 1.72% to 2.70%) for elderly people at home (16 trials).

Mid-Arm Muscle Circumference

The pooled weighted mean difference for percentage mid-arm muscle circumference change from 6 trials showed an increase with supplementation of 1.41% (CI, 0.46% to 2.35%) for patients in the hospital. This difference was not statistically significant for those in long-term care (3 trials) (0.71% [CI, −1.08% to 2.50%]) or at home (6 trials) (0.79% [CI, −1.12% to 2.71%]) (**Appendix Figure 3**, available at www.annals.org).

Discussion

Our review supports the findings of previous meta-analyses that mortality is reduced with protein and energy supplementation, although the reduction is borderline statistically significant. The results are consistent when only high-quality trials are included. The available evidence would suggest that any improved survival is limited to patients who are given oral supplements in the hospital and possibly in long-term care and does not apply to those given supplements in the community. The data also suggest that complications may be reduced for patients in the hospital, although the evidence is limited and weak because of the poor quality of outcome assessment. Hospital stay was not reduced, a finding that may be expected to accompany a reduction in morbidity and complications. These results, together with data from the subgroup analyses, suggest that any effect on mortality and morbidity cannot be generalized for all older patients and settings. We observe a pattern that suggests a reduction in mortality for those who are undernourished at baseline, are 75 years of age or older, and are offered higher energy supplements. The recently published FOOD trial (37) found no difference in death alone and for death and poor outcome together for patients after stroke; however, the vast majority of patients in the trial were not undernourished at baseline. The results of the FOOD trial are consistent with our argument that the effect on mortality is restricted to those with poor nutritional status.

The evidence presented is limited by the poor quality of most of the included trials, particularly in relation to blinding. Few studies used placebo supplements, and bias may have resulted from outcome assessors being aware of treatment status or supplemented patients receiving a higher standard of care. Only 9 trials reported that outcome assessors were blinded. Sixty percent of trials did not report an intention-to-treat analysis, and participants in some studies were excluded from the analysis because they felt unable to take the supplements. The main concern of most trials was the effect of supplementation on nutritional status, and the methods used for assessing change in nutritional status were generally well-reported. However, most trials did not report all the outcomes of interest (**Figure 1**) and may have been selectively reporting some outcomes. The methods used to assess these outcomes were often not adequately described.

The results suggest that supplements can improve the nutritional status of older people. Supplementation produced a small but consistent weight gain, also found in previous reviews, which could be fat, muscle, or water. However, a gain of fat mass or water will not improve muscle strength. The data from mid-arm muscle circumference also suggest a small gain, possibly in muscle mass. Fiatarone and colleagues (36) proposed that exercise is also required to substantially improve muscle strength and function.

Frail elderly patients have low intakes and can find it difficult to consume oral supplements. Indeed, even with extra feeding support from specially trained staff, improvement in the nutritional status of older patients may not be achieved (76). Some trials have reported problems with acceptance of the supplement, which may be associated with the increase in gastrointestinal side effects in some people. The methods of delivery of the supplement were poorly described, however, and the mode and timing of distribution and the volumes offered may be key factors in maximizing acceptance. Certain methods have demonstrated weight and energy gain. Improvements in nutritional intake, particularly for frail older people, have major ethical, organizational, and practical challenges, and the best methods have yet to be established.

Older people are very heterogeneous, with different diagnoses, as reflected in the trials, and some patient groups may be more likely to benefit than others. Patients who are admitted with hip fracture and are more often undernourished on admission may do better with supplementation than patients who are admitted after stroke who may be less undernour-

ished. More work is required to better understand the mechanisms by which the provision of extra nutrients can affect patients with different acute and chronic conditions, possibly through long-term changes in body weight and muscle mass or a more immediate response to an increase in the supply of particular nutrients at a critical stage.

No evidence in our review suggested any improvement in mortality and morbidity for well-nourished people who are given oral supplements of protein and energy. However, trials provide some evidence of increased survival and reduced complications for hospitalized undernourished patients and possibly increased survival for those in long-term care. Although the evidence is limited and is generally of poor quality, we suggest that routine supplements should be considered for this group but not for well-nourished patients. No evidence suggests that providing supplements for those in the community affects mortality and morbidity despite frequent supplement use. Further work in this area is required since adherence to supplementation over longer periods of time may be a particular problem for this group. It is essential to find evidence-based methods to improve the nutritional status of those who are at risk in the community before they become malnourished or are hospitalized.

Our data were limited by the poor quality of most included trials. Future trials should have sufficient statistical power and length of follow-up to detect any beneficial effects, have properly concealed allocation and blinding (particularly for outcome assessment), and perform follow-up for all participants to ensure that those who cannot consume the supplements are included (intention-to-treat analysis). Trials should also focus more on primary outcomes of relevance to patients, such as improvement in function or quality-of-life measures.

From University of Aberdeen, Aberdeen, Scotland, United Kingdom, and Wollongong Hospital, Sydney, Australia.

Acknowledgments: The authors thank the authors who provided further information about the trials; Craig Ramsay and Jonathan Cook, for statistical advice; and Dr. Helen Handoll, who was also involved in the data extraction of trials.

Grant Support: By the Medical Research Council, United Kingdom; Chief Scientist Office of the Scottish Executive Health Department, United Kingdom; and the Student Awards Agency for Scotland, United Kingdom.

Potential Financial Conflicts of Interest: Dr. Potter was principal investigator for a trial included in the review (61).

Requests for Single Reprints: Anne C. Milne, MSc, Health Services Research Unit, Polwarth Building, University of Aberdeen, Aberdeen AB25 2ZD, Scotland, United Kingdom; e-mail, a.c.milne@.abdn.ac.uk.

Current author addresses are available at www.annals.org.

References

1. **Sullivan DH, Sun S, Walls RC.** Protein-energy undernutrition among elderly hospitalized patients: a prospective study. JAMA. 1999;281:2013-9. [PMID: 10359390]
2. **Royal College of Physicians.** Nutrition and Patients: A Doctor's Responsibility. London: Royal College of Physicians; 2003.
3. **Agency for Healthcare Research and Quality.** HCUPnet: A Tool for Identifying, Tracking, and Analyzing Hospital Statistics. Accessed at http://hcup.ahrq.gov/HCUPNet.asp on 30 September 2004.
4. **McWhirter JP, Pennington CR.** Incidence and recognition of malnutrition in hospital. BMJ. 1994;308:945-8. [PMID: 8173401]
5. **Weekes E.** The incidence of malnutrition in medical patients admitted to hospital in south London [Abstract]. Proc Nutr Soc. 1999;58:126A.
6. **Liu L, Bopp MM, Roberson PK, Sullivan DH.** Undernutrition and risk of mortality in elderly patients within 1 year of hospital discharge. J Gerontol A Biol Sci Med Sci. 2002;57:M741-6. [PMID: 12403803]
7. **Sullivan DH, Bopp MM, Roberson PK.** Protein-energy undernutrition and life-threatening complications among the hospitalized elderly. J Gen Intern Med. 2002;17:923-32. [PMID: 12472928]
8. **Sullivan DH, Johnson LE, Bopp MM, Roberson PK.** Prognostic significance of monthly weight fluctuations among older nursing home residents. J Gerontol A Biol Sci Med Sci. 2004;59:M633-9. [PMID: 15215284]
9. **Stratton RJ, Green CJ, Elia M.** Disease-Related Malnutrition: An Evidence-Based Approach to Treatment. Wallingford, UK: CABI Publishing; 2003.
10. **Potter JM.** Oral supplements in the elderly. Curr Opin Clin Nutr Metab Care. 2001;4:21-8. [PMID: 11122555]
11. **Avenell A, Handoll HH.** Nutritional supplementation for hip fracture aftercare in older people. Cochrane Database Syst Rev. 2005:CD001880. [PMID: 15846625]
12. **Alderson P, Green S, Higgins JP.** Cochrane Reviewers Handbook 4.2.2. Chichester, United Kingdom: J Wiley; 2004.
13. **Milne AC, Potter J, Avenell A.** Protein and energy supplementation in elderly people at risk from malnutrition. Cochrane Database Syst Rev. 2005: CD003288. [PMID: 15846655]
14. **Bone, Joint and Muscle Trauma Group.** Cochrane Collaboration Collaborative Review Group (CRG). In: The Cochrane Library, Issue 3, 2005. Chichester, UK: Wiley; 2005.
15. **Sweeting MJ, Sutton AJ, Lambert PC.** What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004;23:1351-75. [PMID: 15116347]
16. **Yusuf S, Peto R, Lewis J, Collins R, Sleight P.** Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis. 1985;27:335-71. [PMID: 2858114]
17. **Deeks JJ, Bradburn MJ, Localio R, Berlin J.** Much ado about nothing: meta-analysis for rare events. Presented at the 6th Cochrane Colloquium, Baltimore, Maryland, 22–26 October 1998.
18. **Higgins JP, Thompson SG, Deeks JJ, Altman DG.** Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60. [PMID: 12958120]
19. **Potter J, Langhorne P, Roberts M.** Routine protein energy supplementation in adults: systematic review. BMJ. 1998;317:495-501. [PMID: 9712593]
20. **Gurney JM, Jelliffe DB.** Arm anthropometry in nutritional assessment: nomogram for rapid calculation of muscle circumference and cross-sectional muscle and fat areas. Am J Clin Nutr. 1973;26:912-5. [PMID: 4727749]
21. **Banerjee AK, Brocklehurst JC, Wainwright H, Swindell R.** Nutritional status of long-stay geriatric in-patients: effects of a food supplement (Complan). Age Ageing. 1978;7:237-43. [PMID: 103378]
22. **Barr SI, McCarron DA, Heaney RP, Dawson-Hughes B, Berga SL, Stern JS, et al.** Effects of increased consumption of fluid milk on energy and nutrient intake, body weight, and cardiovascular risk factors in healthy older adults. J Am Diet Assoc. 2000;100:810-7. [PMID: 10916520]
23. **Benati G, Delvecchio S, Cilla D, Pedone V.** Impact on pressure ulcer healing of an arginine-enriched nutritional solution in patients with severe cognitive impairment. Arch Gerontol Geriatr Suppl. 2001;7:43-7. [PMID: 11431045]
24. **Bonnefoy M, Cornu C, Normand S, Boutitie F, Bugnard F, Rahmani A, et al.** The effects of exercise and protein-energy supplements on body composition and muscle function in frail elderly individuals: a long-term controlled randomised study. Br J Nutr. 2003;89:731-9. [PMID: 12720593]
25. **Bourdel-Marchasson I, Barateau M, Rondeau V, Dequae-Merchadou L, Salles-Montaudon N, Emeriau JP, et al.** A multi-center trial of the effects of oral nutritional supplementation in critically ill older inpatients. GAGE Group.

Groupe Aquitain Geriatrique d'Evaluation. Nutrition. 2000;16:1-5. [PMID: 10674226]
26. **Broqvist M, Arnqvist H, Dahlström U, Larsson J, Nylander E, Permert J.** Nutritional assessment and muscle energy metabolism in severe chronic congestive heart failure—effects of long-term dietary supplementation. Eur Heart J. 1994;15:1641-50. [PMID: 7698134]
27. **Brown KM, Seabrook NA.** Nutritional influences on recovery and length of hospital stay in elderly women following femoral fracture [Abstract]. Proc Nutr Soc. 1992;51:132A.
28. **Bruce D, Laurance I, McGuiness M, Ridley M, Goldswain P.** Nutritional supplements after hip fracture: poor compliance limits effectiveness. Clin Nutr. 2003;22:497-500. [PMID: 14512038]
29. **Carver AD, Dobson AM.** Effect of dietary supplementation of elderly demented hospital residents. J Hum Nutr Diet. 1995;8:389-94.
30. **Collins CE, Kershaw J, Brockington S.** Effect of nutritional supplements on wound healing in home-nursed elderly: a randomized trial. Nutrition. 2005;21:147-55. [PMID: 15723742]
31. **Daniels LA, Miller M, Bannerman E, Whitehead C, Crotty M.** Weight loss post lower limb fracture despite an intensive oral nutrition and exercise intervention [Abstract]. Clin Nutr. 2003;22(Suppl 1):S86.
32. **Deletter MC.** A Nutritional Intervention for Persons with Chronic Airflow Limitation [PhD thesis]. Lexington, KY: Univ of Kentucky; 1991.
33. **Delmi M, Rapin CH, Bengoa JM, Delmas PD, Vasey H, Bonjour JP.** Dietary supplementation in elderly patients with fractured neck of the femur. Lancet. 1990;335:1013-6. [PMID: 1970070]
34. **Edington J, Barnes R, Bryan F, Dupree E, Frost G, Hickson M, et al.** A prospective randomised controlled trial of nutritional supplementation in malnourished elderly in the community: clinical and health economic outcomes. Clin Nutr. 2004;23:195-204. [PMID: 15030959]
35. **Eneroth M, Larsson J, Oscarsson C, Apelqvist J.** Nutritional supplementation for diabetic foot ulcers: the first RCT. J Wound Care. 2004;13:230-4. [PMID: 15214141]
36. **Fiatarone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, et al.** Exercise training and nutritional supplementation for physical frailty in very elderly people. N Engl J Med. 1994;330:1769-75. [PMID: 8190152]
37. **Dennis MS, Lewis SC, Warlow C.** Routine oral nutritional supplementation for stroke patients in hospital (FOOD): a multicentre randomised controlled trial. Lancet. 2005;365:755-63. [PMID: 15733716]
38. **Gariballa SE, Parker SG, Taub N, Castleden CM.** A randomized, controlled, a single-blind trial of nutritional supplementation after acute stroke. JPEN J Parenter Enteral Nutr. 1998;22:315-9. [PMID: 9739036]
39. **Gazzotti C, Arnaud-Battandier F, Parello M, Farine S, Seidel L, Albert A, et al.** Prevention of malnutrition in older people during and after hospitalisation: results from a randomised controlled clinical trial. Age Ageing. 2003;32:321-5. [PMID: 12720620]
40. **Gegerle P, Bengoa JM, Delmi M, Rapin CH, Loizeau E, Vasey H.** [Food survey following femoral neck fracture: effect of a dietetic supplement on nutritional intake]. Schweiz Rundsch Med Prax. 1986;75:933-5. [PMID: 3749675]
41. **Gray-Donald K, Payette H, Boutier V.** Randomized clinical trial of nutritional supplementation shows little effect on functional status among free-living frail elderly. J Nutr. 1995;125:2965-71. [PMID: 7500174]
42. **Hampson G, Martin FC, Moffat K, Vaja S, Sankaralingam S, Cheung J, et al.** Effects of dietary improvement on bone metabolism in elderly underweight women with osteoporosis: a randomised controlled trial. Osteoporos Int. 2003;14:750-6. [PMID: 12904840]
43. **Hankey CR, Summerbell J, Wynne HA.** The effect of dietary supplementation in continuing care elderly people: nutritional, anthropometric and biochemical parameters. J Hum Nutr Diet. 1993;6:317-22.
44. **Hankins C.** Dietary Supplementation with Sustagen in Elderly Patients with Fractured Neck of Femur [MSc thesis]. Sydney, Australia: Sydney Univ; 1996.
45. **Hubsch S, Volkert D, Oster P, Schlierf G.** Effect of dietary supplementation on weight and protein status in undernourished geriatric patients [Abstract]. Clin Nutr. 1992;11:97.
46. **Jensen MB, Hessov I.** Dietary supplementation at home improves the regain of lean body mass after surgery. Nutrition. 1997;13:422-30. [PMID: 9225334]
47. **Knowles JB, Fairbarn MS, Wiggs BJ, Chan-Yan C, Pardy RL.** Dietary supplementation and respiratory muscle performance in patients with COPD. Chest. 1988;93:977-83. [PMID: 3282825]
48. **Krondl M, Coleman PH, Bradley CL, Lau D, Ryan N.** Subjectively healthy elderly consuming a liquid nutrition supplement maintained body mass index and improved some nutritional parameters and perceived well-being. J Am Diet Assoc. 1999;99:1542-8. [PMID: 10608948]
49. **Kwok T, Woo J, Kwan M.** Does low lactose milk powder improve the nutritional intake and nutritional status of frail older Chinese people living in nursing homes? J Nutr Health Aging. 2001;5:17-21. [PMID: 11250664]
50. **Larsson J, Unosson M, Ek AC, Nilsson L, Thorslund S, Bjurulf P.** Effect of dietary supplementation on nutritional status and clinical outcome in 501 geriatric patients—a randomised study. Clin Nutr. 1990;9:179-84.
51. **Lauque S, Arnaud-Battandier F, Mansourian R, Guigoz Y, Paintin M, Nourhashemi F, et al.** Protein-energy oral supplementation in malnourished nursing-home residents. A controlled trial. Age Ageing. 2000;29:51-6. [PMID: 10690696]
52. **Lauque S, Arnaud-Battandier F, Gillette S, Plaze JM, Andrieu S, Cantet C, et al.** Improvement of weight and fat-free mass with oral nutritional supplementation in patients with Alzheimer's disease at risk of malnutrition: a prospective randomized study. J Am Geriatr Soc. 2004;52:1702-7. [PMID: 15450048]
53. **MacFie J, Woodcock NP, Palmer MD, Walker A, Townsend S, Mitchell CJ.** Oral dietary supplements in pre- and postoperative surgical patients: a prospective and randomized clinical trial. Nutrition. 2000;16:723-8. [PMID: 10978851]
54. **Madigan C.** Benefits of Dietary Supplementation in Elderly Patients with Fractured Neck of Femur [MSc dissertation]. Sydney, Australia: Sydney Univ; 1994.
55. **McEvoy AW, James OF.** The effect of a dietary supplement (Build-up) on nutritional status in hospitalized elderly patients. Hum Nutr Appl Nutr. 1982;36:374-6. [PMID: 7141881]
56. **Mcwhirter JP, Pennington CR.** A comparison between oral and nasogastric nutritional supplements in malnourished patients. Nutrition. 1996;12:502-6. [PMID: 8878142]
57. **Meredith CN, Frontera WR, O'Reilly KP, Evans WJ.** Body composition in elderly men: effect of dietary modification during strength training. J Am Geriatr Soc. 1992;40:155-62. [PMID: 1740600]
58. **Ovesen L.** The effect of a supplement which is nutrient dense compared to standard concentration on the total nutritional intake of anorectic patients. Clin Nutr. 1992;11:154-67.
59. **Payette H, Boutier V, Coulombe C, Gray-Donald K.** Benefits of nutritional supplementation in free-living, frail, undernourished elderly people: a prospective randomized community trial. J Am Diet Assoc. 2002;102:1088-95. [PMID: 12171453]
60. **Payette H, Boutier V, Coulombe C.** Efficacy of nutritional intervention in free-living frail elderly. Am J Clin Nutr. 2002;75:340S.
61. **Potter JM, Roberts MA, McColl JH, Reilly JJ.** Protein energy supplements in unwell elderly patients—a randomized controlled trial. JPEN J Parenter Enteral Nutr. 2001;25:323-9. [PMID: 11688936]
62. **Price R, Daly F, Pennington CR, McMurdo ME.** Nutritional supplementation of very old people at hospital discharge increases muscle strength: a randomised controlled trial. Gerontology. 2005;51:179-85. [PMID: 15832045]
63. **Saudny-Unterberger H, Martin JG, Gray-Donald K.** Impact of nutritional support on functional status during an acute exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1997;156:794-9. [PMID: 9309995]
64. **Schols AM, Soeters PB, Mostert R, Pluymers RJ, Wouters EF.** Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. A placebo-controlled randomized trial. Am J Respir Crit Care Med. 1995;152:1268-74. [PMID: 7551381]
65. **Scorer HJ.** The Effect of Nutritional Supplementation with Ensure on the General Health of Undernourished Elderly Patients in the Community. Maidenhead, UK: Abbott Nutrition UK; 1990.
66. **Stableforth PG.** Supplement feeds and nitrogen and calorie balance following femoral neck fracture. Br J Surg. 1986;73:651-5. [PMID: 3742182]
67. **Steiner MC, Barton RL, Singh SJ, Morgan MD.** Nutritional enhancement of exercise performance in chronic obstructive pulmonary disease: a randomised controlled trial. Thorax. 2003;58:745-51. [PMID: 12947128]
68. **Tidermark J, Ponzer S, Carlsson P, Söderqvist A, Brismar K, Tengstrand B, et al.** Effects of protein-rich supplementation and nandrolone in lean elderly women with femoral neck fractures. Clin Nutr. 2004;23:587-96. [PMID: 15297095]
69. **Vermeeren MA, Wouters EF, Geraerts-Keeris AJ, Schols AM.** Nutritional support in patients with chronic obstructive pulmonary disease during hospitalization for an acute exacerbation; a randomized controlled feasibility trial. Clin

Nutr. 2004;23:1184-92. [PMID: 15380912]

70. **Vlaming S, Biehler A, Hennessey EM, Jamieson CP, Chattophadhyay S, Obeid OA, et al.** Should the food intake of patients admitted to acute hospital services be routinely supplemented? A randomized placebo controlled trial. Clin Nutr. 2001;20:517-26. [PMID: 11884000]

71. **Volkert D, Hübsch S, Oster P, Schlierf G.** Nutritional support and functional status in undernourished geriatric patients during hospitalization and 6-month follow-up. Aging (Milano). 1996;8:386-95. [PMID: 9061125]

72. **Woo J, Ho SC, Mak YT, Law LK, Cheung A.** Nutritional status of elderly patients during recovery from chest infection and the role of nutritional supplementation assessed by a prospective randomized single-blind trial. Age Ageing. 1994;23:40-8. [PMID: 8010171]

73. **Wouters-Wesseling W, Wouters AE, Kleijer CN, Bindels JG, de Groot CP, van Staveren WA.** Study of the effect of a liquid nutrition supplement on the nutritional status of psycho-geriatric nursing home patients. Eur J Clin Nutr. 2002;56:245-51. [PMID: 11960300]

74. **Wouters-Wesseling W, Van Hooijdonk C, Wagenaar L, Bindels J, de Groot L, Van Staveren W.** The effect of a liquid nutrition supplement on body composition and physical functioning in elderly people. Clin Nutr. 2003;22:371-7. [PMID: 12880604]

75. **Yamaguchi LY, Coulston AM, Lu NC, Dixon LB, Craig LD.** Improvement in nutrient intake by elderly meals-on-wheels participants receiving a liquid nutrition supplement. Nutrition Today. 1998;33:37-44.

76. **Hickson M, Bulpitt C, Nunes M, Peters R, Cooke J, Nicholl C, et al.** Does additional feeding support provided by health care assistants improve nutritional status and outcome in acutely ill older in-patients?—a randomised control trial. Clin Nutr. 2004;23:69-77. [PMID: 14757395]

Current Author Addresses: Ms. Milne and Dr. Avenell: Health Services Research Unit, Polwarth Building, University of Aberdeen, Aberdeen AB25 2ZD, Scotland, United Kingdom.

Dr. Potter: Acute Geriatric Service, Wollongong Hospital, Level 4 Block C LMB 8808, South Coast Mail Centre 2521, UNSW, Sydney 2052, Australia.

Appendix Table 1. Description of Included Trials*

Study, Year (Reference)	Allocated, n/n†	Assessed, n/n†	Dropout Rate, %‡	Mean Age, y	Environment and Condition	Funding Source	Undernutrition	Duration of Intervention
Banerjee et al., 1978 (21)	33/30	26/24	20	81	Long-stay wards; UK	Support from Glaxo Laboratories Ltd.	Unclear	14 wk
Barr et al., 2000 (22)	101/103	98/102	2	65	Healthy; community; US	International Dairy Foods Association	Unclear	12 wk
Benati et al., 2001 (23)	Unclear	5/5	Unclear	Not given	Cognitive impairment and pressure sores; inpatient; Italy	No data	Unclear	2 wk
Bonnefoy et al., 2003 (24)	28/29	22/20	26	83	≥3 y in retirement homes; frail; France	Grants from INSERM, le Ministère de l'Agriculture et de la Recherche (Programme Aliments Demain), and Laboratoire Diepal	Unclear	9 mo
Bourdel-Marchasson et al., 2000 (25)	295/377	295/377	0	83	Short-term care; inpatient; France	Financed by the Projet Hospitalier de Recherche Clinique, Ministère de la Santé, and the Direction des Hôpitaux	Unclear	≤15 d
Broqvist et al., 1994 (26)	9/13	7/12	14	72	Severe congestive heart failure; possibly outpatient; Sweden	Forenade Mutual Group Life Insurance Company, Lions Research Foundation, Pharmacia AB, The County Council of Östergötland, The Research Foundation of the University Hospital of Linköping, and The Swedish Society of Cardiology	No	8 wk
Brown and Seabrook, 1992 (27)	5/5	5/5	0	Not given	Hip fracture; inpatient; UK	No data	Yes	Until discharge
Bruce et al., 2003 (28)	50/59	47/58	4	84	Hip fracture; inpatient; Australia	No data	No	28 d
Carver and Dobson, 1995 (29)	23/23	20/20	13	77	Dementia; psychogeriatric wards; UK	Mental health unit of Lothian Health Board and Cow & Gate Ltd.	Yes	12 wk
Collins et al., 2005 (30)	18/20	Unclear	Unclear	80	Home-nursed elderly referred for wound management; Australia	Early career grant from the University of Newcastle	No	4 wk
Daniels et al., 2003 (31)	Unclear	Unclear	Unclear	Not given	Postfracture; community; Australia	No data	Yes	6 wk
Deletter, 1991 (32)	37	18/17	5	67	COPD; outpatient; US	Financial support from Ross Laboratories	Yes	9 wk
Delmi et al., 1990 (33)	27/32	Unclear	Unclear	82	Hip fracture; inpatient; Switzerland	No data	Yes	Until discharge
Edington et al., 2004 (34)	51/49	32/26	42	78	Newly discharged from hospital; UK	Abbott Laboratories UK	Yes	8 wk
Eneroth et al., 2004 (35)	26/27	17/23	25	74	Patients > 60 y of age with diabetes mellitus and Wagner grade I–II foot ulcer >4-wk duration	Grant from Nutricia AB	No	6 mo
Fiatarone et al., 1994 (36)	24/26	Unclear	Unclear	87	Can walk 6 m; long-term care; US	Supported in part by National Institute on Aging (UO1 AG09078), U.S. Department of Agriculture, U.S. Public Health Service, Brookdale Foundation, Ross Foundation, and Keiser Sports Health Equipment	No	10 wk
FOOD trial, 2005 (37)	2016/2007	2012/2000	0	71	Inpatients with stroke who could swallow; multinational	Health Technology Assessment UK; Stroke Association; Chief Scientist Office Scotland; Chest, Heart and Stroke Association; and Royal Australasian College of Physicians	No	Until discharge
Gariballa et al., 1998 (38)	21/21	18/13	26	79	Stroke; short-term care; inpatient; UK	No data	Yes	4 wk
Gazzotti et al., 2003 (39)	39/41	39/41	0	80	Short-term care; inpatient; Belgium	Coauthor from Nestlé Clinical Nutrition Paris	Yes	8 wk
Gegerle et al., 1986 (40)	7/9	Unclear	Unclear	77	Hip fracture; inpatient; Switzerland	No data	Unclear	Until discharge
Gray-Donald et al., 1995 (41)	25/25	22/24	8	78	Community; Canada	National Health Research and Development Program, Canada	Yes	12 wk
Hampson et al., 2003 (42)	36/35	31/33	10	76	Osteoporosis; community; UK	Charity Action Research	Yes	8 wk
Hankey et al., 1993 (43)	10/10	7/7	30	81	Inpatient rehabilitation; UK	No data	Yes	8 wk
Hankins, 1996 (44)	17/15	17/14	3	86	Hip fracture; inpatient; Australia	No data	Yes	30 d
Hubsch et al., 1992 (45)	16/16	16/16	0	>75	Geriatric; inpatient; Germany	No data	Yes	Until discharge
Jensen and Hessov, 1997 (46)	Unclear	14/20	Unclear	Not given	Postsurgery; community; Denmark	The Health Insurance Foundation and Danish Cancer Society and an ESPEN fellowship donated by Abbott Laboratories	Unclear	110 d
Knowles et al., 1988 (47)	13/12	13/12	0	69	Severe COPD; metabolic unit; Canada	Three authors supported by a grant from Mead Johnson Nutritionals	Unclear	8 wk
Krondl et al., 1999 (48)	35/36	35/36	0	70	Community; Canada	One author was employed by Mead Johnson Nutritionals	No	16 wk
Kwok et al., 2001 (49)	28/24	25/20	13	80	Nursing homes; Hong Kong	None reported	Yes	7 wk
Larsson et al., 1990 (50)	197/238	Unclear	Unclear	80	Newly admitted to long-term care; Sweden	Swedish Medical Council and County of Östergötland Research Fund	Subgroup	Up to 8 wk
Lauque et al., 2000 (51)	19/22	13/22	15	84	Nursing homes; France	Two authors from Nestlé France and Switzerland	Yes	60 d
Lauque et al., 2004 (52)	46/45	Unclear	Unclear	79	Geriatric wards and daycare centers; France	Nestlé Clinical Nutrition	Yes	3 mo
MacFie et al., 2000 (53)	24/24/27/25	24/24/27/25	0	65	GI surgery; outpatient and inpatient; UK	None reported	No	Before and/or after elective surgery
Madigan, 1994 (54)	Unclear	18/12	Unclear	79	Hip fracture; inpatient; Australia	Not reported	No	10 d
McEvoy and James, 1982 (55)	26/25	26/25	0	Not given	Short-term care; inpatient; UK	None reported	Yes	4 wk
Mcwhirter and Pennington, 1996 (56)	35/26	35/26	0	71	Inpatient; UK	Supported by Clinitec Nutrition Ltd.	Yes	≥7 d
Meredith et al., 1992 (57)	6/6	6/5	8	66	Healthy; metabolic unit; US	USDA Research Center at Tufts University, Ross Laboratories, and University of California	No	12 wk
Ovesen, 1992 (58)	17/17	10/14	29	74	Chronic disease; inpatient; Denmark	None reported	Yes	10 d
Payette et al., 2002 (59)	43/46	41/42	7	79	Needing home help; community; Canada	None reported	Yes	16 wk
Payette et al., 2002 (60)	Unclear	50/49	Unclear	79	Needing meals-on-wheels; community; Canada	University–industry grant from MRC of Canada and Nestec Ltd.	Yes	24 wk
Potter et al., 2001 (61)	186/195	165/162	14	Median, 83	Short-term care; inpatient; UK	Scottish Office Home and Health Department	Subgroup	Until discharge
Price et al., 2005 (62)	66/70	35/41	44	85	Undernourished elderly patients after discharge from hospital into the community	None reported	Yes	8 wk
Saudny-Unterberger et al., 1997 (63)	17/16	14/10	27	69	COPD; inpatient; Canada	Supported by Quebec Lung Association and the Research Center of the Montreal Chest Clinic	Unclear	14 d
Schols et al., 1995 (64)	72/63	72/63	0	65	COPD; rehabilitation center; the Netherlands	None reported	Unclear	8 wk
Scorer, 1990 (65)	Unclear	48/46	Unclear	76	Community, UK	Abbott UK	Yes	12 wk
Stableforth, 1986 (66)	Unclear	Unclear	Unclear	82	Hip fracture; inpatient; UK	South West Regional Hospital Board	No	10 d
Steiner et al., 2003 (67)	42/43	25/35	29	67	Pulmonary rehabilitation; inpatient; UK	Partial financial support covering dietetic support and consumables	No	7 wk
Tidermark et al., 2004 (68)	20/20	18/17	13	84	Hip fracture; inpatient; Sweden	Trygg-Hansa Insurance Company, Swedish Orthopedic Association, Swedish Research Council, Novo Nordic Fund, Nutricia Nordica AB, and Nycomed AB	Yes	6 mo
Vermeeren et al., 2004 (69)	29/27	Unclear	Unclear	67	COPD; inpatients; the Netherlands	Numico Research BV	Yes	Until discharge
Vlaming et al., 2001 (70)	275/274	271/274	1	66	Short-term care; medical or surgical inpatient; UK	North Thames NHS R&D and supplementary financial support from Abbott Laboratories	Yes	Until discharge
Volkert et al., 1996 (71)	35/37	20/26	36	85	Short-term care; inpatient; Germany	In part by Bundesministerium für Gesundheit and Fa.B. Braun	Yes	6 mo
Woo et al., 1994 (72)	40/41	Variable	Variable	73	After inpatient chest infection; community; Hong Kong	Sandoz Foundation for Gerontological Research and University and Polytechnic Grant Committee	Unclear	1 mo
Wouters-Wesseling et al., 2002 (73)	21/21	19/16	17	82	Dementia; psychogeriatric nursing homes; the Netherlands	Numico Research BV and Nutricia	Yes	3 mo
Wouters-Wesseling et al., 2003 (74)	52/49	34/34	33	81	Residence or sheltered housing for older people; the Netherlands	Numico Research BV	No	6 mo
Yamaguchi et al., 1998 (75)	32/30	11/6	73	78	Homebound starting meals-on-wheels; community; US	Partly funded by Ross Products Division, Abbott Laboratories	Yes	18 mo

* COPD = chronic obstructive pulmonary disease; ESPEN = European Society for Parenteral and Enteral Nutrition; FOOD = Feed Or Ordinary Diet; MRC = Medical Research Council; NHS R&D = National Health Service Research and Development; UK = United Kingdom; US = United States; USDA = U.S. Department of Agriculture.
† Intervention/control.
‡ Percentage of withdrawals, dropouts, and those excluded after randomization.

Appendix Table 2. Description of Included Trials, Continued*

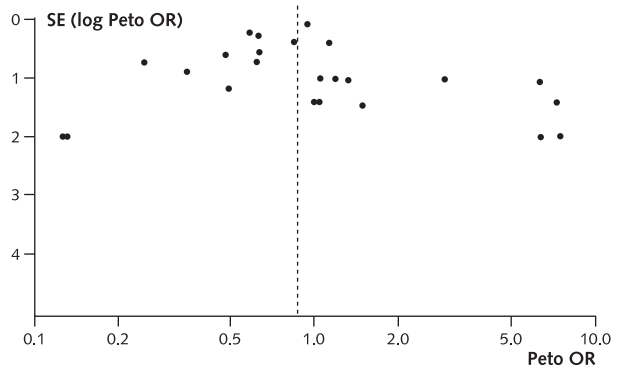
Study, Year (Reference)	Energy and Protein Content†	Allocation Concealment‡	ITT§	Blinding of Outcome Assessors‖	Total Quality Score¶	Outcomes**	Morbidity and Complications	Adverse Effects
Banerjee et al., 1978 (21)	265 kcal and 18.6 g of protein daily	1	2	0	6	Mortality, anthropometry, and dietary intake	No data	No data
Barr et al., 2000 (22)	24 oz of low-fat milk daily	1	1	0	7	Weight, functional status, quality of life, and dietary intake	No data	No data
Benati et al., 2001 (23)	500 kcal and 37 g of protein daily	1	0	0	2	Complications	More rapid improvement in pressure ulcer healing in treatment group (no numerical data provided)	No data
Bonnefoy et al., 2003 (24)	400 kcal and 30 g of protein daily	2	1	0	15	Functional status, anthropometry, and adherence	No data	No data
Bourdel-Marchasson et al., 2000 (25)	400 kcal and 30 g of protein daily	1	2	1	8	Mortality, complications, and dietary intake	Incidence of pressure ulcers, not suitable for meta-analysis	No data
Broqvist et al., 1994 (26)	750 kcal and 30 g of protein daily	1	2	2	14	Mortality, complications, weight, anthropometry, and dietary intake	NYHA functional class, death, renal failure, and diabetic coma	No data
Brown and Seabrook, 1992 (27)	Replenish energy and protein deficit	0	2	2	7	Mortality, length of stay, functional status, anthropometry, weight, and dietary intake	No data	No data
Bruce et al., 2003 (28)	352 kcal and 17.6 g of protein daily	0	1	0	9	Mortality, length of stay, functional status, anthropometry, weight, and adherence	Percentage of patients who died or were in nursing home	No data
Carver and Dobson, 1995 (29)	600 kcal/d and protein	0	1	1	13	Mortality, weight, anthropometry, and adherence	No data	No data
Collins et al., 2005 (30)	473 kcal and 19.8 g of protein daily or 237 kcal and 8.8 g of protein daily	1	0	1	14	Dietary intake, cognitive function, quality of life, and wound healing	Incomplete wound healing: wound area, wound depth, and exudate amount	No data
Daniels et al., 2003 (31)	Details unclear	1	0	0	3	Functional status, adherence, and weight	No data	No data
Deletter, 1991 (32)	Details unclear	1	2	0	8	Functional status, weight, anthropometry, and dietary intake	No data	No data
Delmi et al., 1990 (33)	254 kcal and 20.4 g of protein daily	1	1	0	10	Mortality, complications, side effects, length of stay, and dietary intake	Total (excluding deaths), bedsore, severe anemia, cardiac failure, infection, GI ulcer, and other	No side effects
Edington et al., 2004 (34)	Choice of supplements giving 600–1000 kcal/d and protein	2	1	0	8	Mortality, functional status, quality of life, anthropometry, weight, and dietary intake	No data	No data
Eneroth et al., 2004 (35)	400 kcal/d and protein, choice of flavors	1	1	2	14	Mortality, wound healing, amputations, nutritional status, and adherence	Wound healed at 6 mo and amputations	Nausea and vomiting in 3/26
Fiatarone et al., 1994 (36)	360 kcal/d and protein	1	2	0	16	Mortality, functional status, side effects, weight, anthropometry, and dietary intake	No data	Diarrhea in 2/49
FOOD trial, 2005 (37)	540 kcal and 62.5 g of protein daily	2	2	0	11	Mortality or poor outcome, length of stay, quality of life, complications, and residence at follow-up	Total pressure sores, poor outcome (MRS score, 3–5), and number with recovery or improvement	Treatment stopped because of poor glycemic control in 33/2016 in the intervention group
Gariballa et al., 1998 (38)	600 kcal and 20 g of protein daily	2	2	1	10	Mortality, complications, length of stay, discharge destination, functional status, weight, anthropometry, and dietary intake	Infective complications	No data
Gazzotti et al., 2003 (39)	500 kcal and 21 g of protein daily	1	1	0	7	Mortality, length of stay, side effects, weight, and dietary intake	Rehospitalized (no denominators)	Loss of appetite, nausea, or diarrhea in 5/39
Gegerie et al., 1986 (40)	254 kcal and 20 g of protein daily	1	2	0	7	Dietary intake	No data	No data
Gray-Donald et al., 1995 (41)	500–700 kcal and 17–26 g of protein daily	1	2	1	10	Mortality, quality of life, functional status, handgrip, anthropometry, weight, and dietary intake	No data	No data
Hampson et al., 2003 (42)	300–600 kcal and 12–24 g of protein daily	2	1	0	9	Mortality, functional status, weight, and dietary intake	Too ill to continue	No data
Hankey et al., 1993 (43)	Details unclear	1	0	0	6	Anthropometry, weight, dietary intake	No data	No data
Hankins, 1996 (44)	409 kcal and 22.5 g of protein daily	2	2	0	12	Mortality, complications, side effects, length of stay, functional status, weight, anthropometry, and dietary intake	Total complications excluding deaths	Dysphagia, nausea, diarrhea, and fatigue were reasons for dropout in 4/17
Hubsch et al., 1992 (45)	238 kcal and 20 g of protein daily	1	2	0	4	Mortality and weight	No data	No data
Jensen and Hessov, 1997 (46)	Choice of supplements to achieve 1.5 g of protein/kg of body weight	2	1	1	9	Anthropometry, weight, and dietary intake	No data	No data
Knowles et al., 1988 (47)	To increase calories to >50% of normal; with protein	1	2	2	10	Functional status, anthropometry, and dietary intake	No data	No data
Krondl et al., 1999 (48)	235 kcal and 11.8 g of protein daily	0	0	0	8	Mortality, quality of life, weight, and dietary intake	No data	No data
Kwok et al., 2001 (49)	Milk supplement; details unclear	1	1	2	10	Mortality, functional status, anthropometry, weight, dietary intake, and side effects	No data	No participants developed diarrhea
Larsson et al., 1990 (50)	400 kcal and 16 g of protein daily	2	0	0	5	Mortality, complications, and functional status	Development of pressure sores after admission, pressure sores healed, total number of sores, and improvement in Norton scale	No data
Lauque et al., 2000 (51)	300–500 kcal and up to 37.5 g of protein/d	1	1	0	9	Mortality, functional status, weight, and dietary intake	Yes, no denominators	No data
Lauque et al., 2004 (52)	Between 300 and 500 kcal/d and up to around 21 g/d of protein	1	0	0	8	Mortality, functional status, weight, body composition, and dietary intake	Hospitalization, no denominators provided for fractures or pressure ulcers	No data
MacFie et al., 2000 (53)	500–600 kcal and 10–20 g of protein daily	2	1	0	10	Mortality, complications, length of stay, side effects, functional status, quality of life, anthropometry, weight, and dietary intake	Total complications excluding deaths	Postoperative nausea with supplements in 8/75 in the intervention group vs. 0/25 in the control group
Madigan, 1994 (54)	310 kcal and 16 g of protein daily	1	0	0	5	Mortality, complications, length of stay, functional status, anthropometry, dietary intake, and adherence	Too ill to continue	No data
McEvoy and James, 1982 (55)	644 kcal and 36.4 g of protein daily	1	2	0	5	Mortality, anthropometry, weight, and side effects	No data	Malabsorption in 6/26 in the intervention group and 5/25 in the control group
Mowhirter and Pennington, 1996 (56)	Aim to meet nutritional needs	1	2	0	8	Side effects, weight, anthropometry, and dietary intake	No data	No side effects
Meredith et al., 1992 (57)	8 kcal and 0.33 g of protein daily, per kg ideal body weight	1	1	0	10	Mortality, functional status, anthropometry, weight, and dietary intake	No data	No data
Ovesen, 1992 (58)	At least 800 kcal and 32 g of protein daily	1	1	1	12	Mortality, side effects, dietary intake, and adherence	No data	10/37 excluded because of GI discomfort attributed to the supplements
Payette et al., 2002 (59)	Maximum tolerable intake to gain 0.5 kg of body weight per wk	1	2	1	9	Mortality, weight, dietary intake, functional status, anthropometry, and quality of life	Yes, no denominators	No data

Appendix Table 2—Continued

Study, Year (Reference)	Energy and Protein Content†	Allocation Concealment‡	ITT§	Blinding of Outcome Assessors‖	Total Quality Score¶	Outcomes**	Morbidity and Complications	Adverse Effects
Payette et al., 2002 (60)	To achieve 100% of energy and protein requirements	1	0	1	6	Functional status, anthropometry, weight, and dietary intake	No data	No data
Potter et al., 2001 (61)	540 kcal and 22.5 g of protein daily	2	2	1	12	Mortality, complications, length of stay, functional status, anthropometry, weight, and dietary intake	Infective complications	No side effects
Price et al., 2005 (62)	600 kcal and 24 g of protein daily	2	2	0	9	Mortality, complications, functional status, anthropometry, weight, and dietary intake	Unplanned readmissions; ≥1 prescription of antibiotics, new antidepressant prescriptions, or introduction of other new medication; outpatient or day of hospital attendance; respite admission; falls; planned admissions; and admissions to residential home	GI disturbances (vomiting, diarrhea, constipation, nausea, or hematemesis)
Saudny-Unterberger et al., 1997 (63)	1.5 × resting energy expenditure and 1.7 × BMI < 20 kg/m^2	2	1	1	9	Mortality, complications, length of stay, functional status, quality of life, anthropometry, weight, and dietary intake	Too ill to continue	No side effects
Schols et al., 1995 (64)	420 kcal and 14 g of protein daily	1	1	2	11	Mortality, functional status, anthropometry, weight, dietary intake, and side effects	No data	No data
Scorer, 1990 (65)	3 cans/d	1	0	0	7	Quality of life and weight	No denominators	No data
Stableforth, 1986 (66)	320 kcal and 18.5 g of protein daily	1	1	0	7	Mortality, complications, and dietary intake	Surgical, GI, and urinary complications	Intolerance to supplements proved to be a handicap in correcting the deficits in many patients
Steiner et al., 2003 (67)	570 kcal and 28 g of protein daily	2	2	1	17	Mortality, complications, functional status, anthropometry, weight, dietary intake, and adherence	Exacerbation of COPD	No data
Tidermark et al., 2004 (68)	Details unclear	2	2	1	13	Mortality, length of stay, complications, functional status, side effects, adherence, weight, and anthropometry	Fracture healing complications, infectious wound complications, and urinary tract infection	No side effects
Vermeeren et al., 2004 (69)	570 kcal and 27 g of protein daily	1	0	2	15	Weight, complications, functional status, dietary intake, and side effects	Rehospitalized within 3 mo	Nausea and vomiting in 3/29 in the intervention group vs. 1/27 in the control group
Vlaming et al., 2001 (70)	600 kcal and 25 g of protein daily	2	2	2	14	Mortality and length of stay	No data	No data
Volkert et al., 1996 (71)	500 kcal and 30 g of protein daily	1	1	0	10	Mortality, functional status, anthropometry, weight, dietary intake, and adherence	No data	No data
Woo et al., 1994 (72)	500 kcal and 17 g of protein daily	1	2	2	12	Mortality, functional status, anthropometry, weight, and dietary intake	No denominators	No data
Wouters-Wesseling et al., 2002 (73)	250 kcal and 8.5 g of protein daily	1	1	0	14	Mortality, functional status, side effects, adherence, weight, and dietary intake	No data	No denominators
Wouters-Wesseling et al., 2003 (74)	250 kcal and 8.8 g of protein daily	0	1	0	14	Mortality, functional status, quality of life, weight, adherence, and dietary intake	Too ill to continue	No data
Yamaguchi et al., 1998 (75)	600 kcal and 30 g of protein daily	2	0	0	12	Weight and dietary intake	No data	No data

* BMI = body mass index; COPD = chronic obstructive pulmonary disease; FOOD = Feed Or Ordinary Diet; GI = gastrointestinal; ITT = intention-to-treat; MRS = modified Rankin scale; NYHA = New York Heart Association.
† Composition of supplement, if reported.
‡ Allocation concealed: 2 = method did not allow disclosure of assignment; 1 = small but possible chance of disclosure or states random but no description; 0 = quasi-randomized.
§ ITT analysis: 2 = carried out for all possible cases; 1 = states number and reasons for withdrawal, but ITT was not possible; 0 = not mentioned or not possible.
‖ Blinding of outcome assessors: 2 = action taken or outcomes such that bias unlikely; 1 = small or moderate chance of unblinding of assessors; 0 = not mentioned.
¶ From a possible score of 20.
** Data unavailable or incomplete for some outcomes. Results from dietary intake not reported here.

Appendix Figure 1. **Funnel plot.**



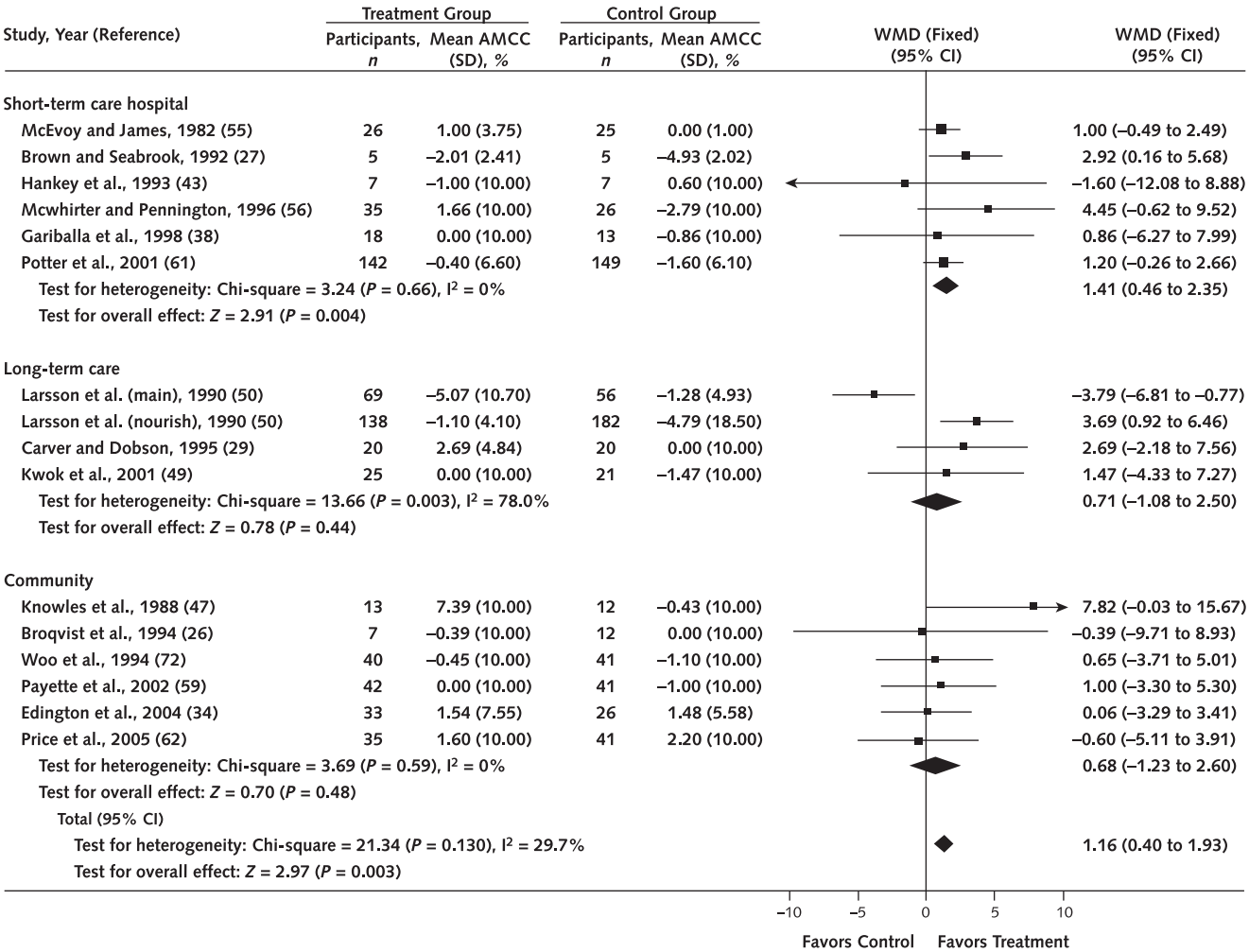
OR = odds ratio.

Appendix Figure 2. **Meta-analysis of length of stay (*LOS*).**

Study, Year (Reference)	Treatment Group Participants, *n*	Treatment Group Mean LOS (SD), *d*	Control Group Participants, *n*	Control Group Mean LOS (SD), *d*	WMD (Random) (95% CI)	WMD (Random) (95% CI)
Undernourished at baseline						
Brown and Seabrook, 1992 (27)	5	27.00 (5.00)	5	48.00 (18.50)		−21.00 (−37.80 to −4.20)
Hankins, 1996 (44)	17	24.00 (15.10)	14	26.00 (19.30)		−2.00 (−14.40 to 10.40)
Gariballa et al., 1998 (38)	20	24.00 (30.00)	20	42.00 (18.50)		−18.00 (−33.45 to −2.55)
Potter et al. (moderately undernourished), 2001 (61)	82	18.50 (35.00)	74	16.50 (15.00)		2.00 (−6.31 to 10.31)
Potter et al. (severely undernourished), 2001 (61)	29	17.00 (24.00)	26	17.50 (18.50)		−0.50 (−11.76 to 10.76)
Vlaming et al., 2001 (70)	274	14.20 (24.90)	274	11.40 (16.40)		2.80 (−0.73 to 6.33)
Tidermark et al., 2004 (68)	18	20.00 (88.00)	17	27.00 (48.00)		−7.00 (−53.62 to 39.62)
Test for heterogeneity: Chi-square = 13.82 (*P* = 0.030), I^2 = 56.6%						−3.30 (−9.64 to 3.05)
Test for overall effect: *Z* = 1.02 (*P* = 0.31)						
Nourished at baseline						
Delmi et al., 1990 (33)	21	24.00 (36.00)	28	40.00 (62.00)		−16.00 (−43.65 to 11.65)
Madigan, 1994 (54)	18	16.00 (8.00)	12	16.00 (11.00)		1.00 (−6.24 to 8.24)
MacFie et al., 2000 (53)	75	11.00 (10.00)	26	13.00 (10.00)		−2.00 (−6.53 to 2.53)
Potter et al. (nourished), 2001 (61)	54	13.50 (15.00)	82	21.00 (16.76)		−7.50 (−13.28 to −1.72)
Bruce et al., 2003 (28)	50	17.70 (9.40)	68	16.80 (9.20)		1.10 (−2.42 to 4.62)
FOOD trial, 2005 (37)	2011	34.00 (48.00)	2001	32.00 (46.00)		2.00 (−0.88 to 4.88)
Test for heterogeneity: Chi-square = 10.81 (*P* = 0.060), I^2 = 53.7%						−0.84 (−3.91 to 2.23)
Test for overall effect: *Z* = 0.54 (*P* = 0.59)						
Total (95% CI)						
Test for heterogeneity: Chi-square = 24.79 (*P* = 0.020), I^2 = 51.6%						−1.17 (−3.90 to 1.57)
Test for overall effect: *Z* = 0.84 (*P* = 0.40)						

FOOD = Feed Or Ordinary Diet; WMD = weighted mean difference.

Appendix Figure 3. **Meta-analysis of percentage of arm muscle circumference change (*AMCC*).**



WMD = weighted mean difference.