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**"ECONOMIC EVALUATION FOR PROTEIN AND ENERGY SUPPLEMENTATION IN ADULTS: OPPORTUNITIES TO STRENGTHEN THE EVIDENCE"**

**Running Title**

Economic evaluation protein energy supplementation

**ABSTRACT**

Malnutrition is a costly problem for health care systems internationally. Malnourished individuals require longer hospital stays and more intensive nursing care than adequately nourished individuals and have been estimated to cost an additional £7.3 billion in health care expenditures in the United Kingdom alone. However, treatments for malnutrition have rarely been considered from an economic perspective. The aim of this systematic review was to identify the cost effectiveness of using protein and energy supplementation, as a widely used intervention to treat adults with and at risk of malnutrition. Papers were identified that included economic evaluations of protein or energy supplementation for the treatment or prevention of malnutrition in adults. While the variety of outcome measures reported for cost effectiveness studies made synthesis of results challenging, cost benefit studies indicated that the savings for the health system could be substantial due to reduced lengths of hospital stay and less intensive use of health services after discharge. In summary the available economic evidence indicates that protein and energy supplementation in treatment or prevention of malnutrition provides an opportunity to improve patient wellbeing and lower health system costs.

**Keywords**

Review, Costs and Cost Analysis, Enteral Nutrition, Malnutrition, Oral nutritional supplementation

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**INTRODUCTION**

Malnutrition is a costly problem for health care systems internationally.[1] In Australia, the additional cost of malnutrition to the Victorian public health system has been recently estimated as $10.7 million per year with the authors noting that this is likely to greatly underestimate the true costs.[2] In the UK the annual cost to the health system has been estimated at more than £7.3 billion, mostly due to increased costs of hospital and long-term care.[1] It has been identified that up to 55% of hospital patients at any one point in time are malnourished.[3-5] In addition, up to 50% of residential care and 30% of community living elderly have been found to be malnourished.[3,6-8] The consequences of malnutrition upon an individual's health are severe and impact negatively upon health care expenditure through increases in the frequency and duration of hospital episodes, and increased intensity of health and community service utilization following discharge from hospital.[9-13]

Containment of increasing health care expenditures is a global phenomenon and increasingly economic evaluation is being utilised as a tool for demonstrating the efficiency or value for money of health care expenditures. In a world of increasing resource constraints for health care expenditures, demonstrating not only the clinical effectiveness but also the cost effectiveness of nutrition interventions for the treatment of malnutrition in adult populations in hospital, residential and community settings is becoming a key evidential requirement for health care decision-makers. Whilst previous reviews[9] have highlighted the clinical effectiveness of interventions for the treatment of malnutrition, no review to date has systematically sought to identify and report upon the quality of, the economic evaluation methods used in published studies of treatments for malnutrition.

Previous studies have identified the most common treatments for malnutrition are strategies to increase energy and protein intake via the normal oral route, such as enriched diets, high energy and protein snacks and oral nutrition supplements.[14] Therefore, our primary aim was to undertake a systematic review to identify economic evaluation studies of protein and energy supplementation for the treatment of people with or at risk of malnutrition. A secondary aim was to provide an overview of the quality of the economic evidence available on this topic.

## METHODS

### Defining and categorising economic evaluation

Economic evaluation may be defined as the comparative analysis of alternative courses of action in terms of both their costs and consequences.[15] Therefore the fundamental requirements of any economic evaluation are to identify, measure, value and compare the costs and consequences of the alternatives being considered. There are five generally accepted forms of economic evaluation for health care interventions which are described in Table 1.[16,17] Briefly they are cost-minimisation analysis, cost-benefit analysis, cost-consequence analysis, cost-effectiveness analysis, and cost-utility analysis. It is appropriate to conduct a cost minimisation analysis of a health care intervention only where there is sound evidence (e.g. through the findings of a well conducted randomised controlled trial) to indicate that there is no difference in outcomes for both effectiveness and safety between the intervention under consideration and the most appropriate alternative intervention.[18] Within cost benefit analysis both costs and benefits are measured and valued in monetary terms to determine the net benefit of the new intervention e.g. as a consequence of reductions in future health care costs due to decreases in morbidity and/or mortality. On the other hand cost-consequence, cost-effectiveness, and cost-utility analysis all compare the benefits of interventions through a focus upon changes in clinical and/or patient focused outcomes. A cost-effectiveness analysis (CEA) involves a direct comparison of the costs associated with an intervention with a single measure of effectiveness which is usually clinically or bi-medically focused. This allows the calculation of an incremental cost effectiveness ratio (ICER) where the additional costs of the treatment are divided by additional benefits of providing the treatment e.g. cost per one unit improvement in blood cholesterol levels. Cost consequence analysis is a form of economic evaluation where the incremental costs associated with the new intervention are calculated and a series of outcomes or consequences are presented but the costs and outcomes are not presented together in the form of a ratio. Cost-utility analysis (CUA) is a particular form of CEA which warrants special consideration as it is explicitly the preferred method of economic evaluation for many health regulatory bodies in Australia (Pharmaceutical Benefits Advisory Committee (PBAC)), United Kingdom (National Institute for Health and Clinical Excellence) and many other bodies around the world.[18-19] Within CUA benefits are measured and valued using 'utility', where this reflects preference for a particular health state.[20] Once measured, the utility of a particular health state or series of health states can be combined with the quantity or number of life years a person spends in the health state to give an indicator of the Quality Adjusted Life Years (QALY) attributable to an intervention and ultimately a ICER of cost per QALY gained. There are many ways of measuring utility, but a commonly utilised method is through the use of a multi-attribute utility instrument (MAUI).[21] A MAUI is a validated instrument that provides both a framework to describe health states for valuation, and can have a developed algorithm to convert those health states into utility weights or values which indicate the preference of the population for those health states. Generally a value of one is assigned for a health state representing perfect health, zero for death, with other health states falling on a continuum between these two points. Negative values indicating a health state perceived as worse than death can be possible. It is these utility values which can be combined with the length of time a person spends in a health state to determine QALY. There are a number of MAUI which have been developed in different populations, but some of the most common include EQ-5D, Short Form 6D, Health Utilities Indexes, and Quality of Well-Being.[15] The scales have different advantages and disadvantages depending on the attributes of health included in the scale, and the number of levels of ability or impairment for each of the attributes which need to be appropriately matched to the population being studied and the expected impact of the intervention.[21] However, the advantage the MAUI share in measuring utility is they cover not only the expected effects of the intervention on mobility or pain for example, but also the flow on effects to independence, and ability to carry out your usual role within society. MAUI therefore have the opportunity to track the effects of interventions more broadly than through traditional clinical outcomes, and allow comparisons of interventions targeting different outcomes, for example providing medications for asthma compared to controlling hyperlipidaemia. This flexibility in application and interpretation has led to CUA using MAUIs being the most preferred method of economic evaluation. Many regulatory bodies for health have a threshold (either explicit or not) for the cost per QALY ICER below which interventions are likely to be considered cost effective, such as the National Institute for Health and Clinical Excellence which recommends cost per QALY ICER's below £20,000.[19]

**Search Strategy**

A search strategy was developed largely replicating that published by Milne et al.[9] in their review of protein and energy supplementation for treatment of malnutrition in older adults, but with additional search terms to identify studies including economic evaluation (see Appendix 1 in supplementary information). While the review published by Milne et al.[9]

originally dealt with only older adults (average age 65 years and above), due to the paucity of economic evidence we widened our search strategy to include all adults (18 years and above) thereby facilitating a broader analysis of the quality of the economic literature. Inclusion criteria are as follows. We included hospitalised, residential aged care and community dwelling populations. We focused specifically upon economic evaluation studies reported either as stand-alone papers or as components of papers which also included a broader focus upon clinical effectiveness. Interventions of interest were those aiming to increase the energy and protein levels of individuals via oral administration. Interventions which included a mix of interventions such as nutrition screening and assessment, dietary advice, and feeding assistance in addition to protein and energy supplementation were included. Types of studies included were any comparative study, including randomised controlled trials, and non-randomised controlled trials. Studies employing economic modelling methods were also included. Exclusion criteria included trials purely based on patients in critical care or recovering from cancer treatment as these patients typically have highly specialised nutritional needs. In addition trials of specialised nutrition components such as specific amino acids or immunomodulatory components were excluded due to differences in the effect and cost data for these products. Relevant comparators included 'usual practice' (i.e. ad hoc dietary care or a different nutritional supplement with different energy and protein content) or a 'placebo' (such as a low energy drink).

Databases searched included Cochrane register of Controlled Trials (until December 2012), Medline (from 1946 until December 2012), Scopus (until December 2012), Web of Knowledge (until December 2012), CINAHL (until December 2012) and Australasian Medical Index (until December 2012).

In addition, any reviews of the topic that were identified through the above methods were checked for additional studies that had not been previously identified. Reference lists of identified articles or reviews of protein and energy supplementation or evaluation of nutrition therapy were also checked for additional references.

**Data Collection and Analysis**

Two reviewers independently identified studies from the search results for further analysis by scanning the title, abstract, and key words of the studies for evidence that they compared a protein and energy supplemented diet with no intervention, a placebo, or an alternative supplement and involved adult participants. If there was any doubt about the eligibility of the article, it was also retrieved for further investigation.

All information was extracted independently by the two reviewers. All differences in extraction were clarified with a third reviewer by going back to the original article. Information extracted included: study design, participants, intervention, sample size, follow up period, results, sensitivity analysis (which measures the variability around the base-case results), and discounting of future costs and benefits (where applicable).[15] The quality of the economic evaluations in the articles was assessed using the 35 point checklist developed by Drummond and colleagues for quality submission of economic evaluations to journals.[15] These criteria assess the quality of the economic evaluation in terms of study design, data collection, analysis and interpretation of results, and allow assessment of economic evaluations based on single trial data and combinations of data into economic models. Similarly to the previous review, we did not exclude studies based on the nutritional status of the participants, but identified studies were categorised into one of two groups according to whether they had targeted malnourished patients only (according to the criteria within the paper) or did not specify the nutritional status of their participants for entry to the study for ease of interpretation and reporting of results.

## RESULTS

### Description of Studies

2,750 titles were identified through the search (Figure 1). Of those titles, the vast majority could be excluded via reading the titles or the abstract (2,632 out of the 2,750), as their focus was not health care but agricultural practices or animal health or manufacturing of food, or did not include an intervention to increase dietary energy or protein. A total of 118 papers had the full text of the title accessed and of those a further 100 were excluded due to lack of an intervention to increase energy and protein intake via the normal oral route (e.g. included parental nutrition or naso-gastric, naso-enteric, or percutaneous endoscopic gastrostomy (PEG) feeding (n=15), did not include economic outcomes (n=32), did not include a dietary intervention to increase energy or protein (n=47) or were testing supplementation of immunomodulatory components within a protein and energy supplement (n=6). Two papers were protocols for studies not yet published and were therefore excluded. This left 16 papers focused upon economic evaluation which were included in the review.

### Results of studies where participants were defined as malnourished

Six studies targeted malnourished patients using a variety of identification methods (e.g. Subjective Global Assessment, Mini Nutritional Assessment, BMI, history of unplanned weight loss), listed in Table 2. Of those studies three were cost utility studies,[22,23,24] with the remaining studies being cost benefit analyses[25,26] and a cost consequence analysis respectively.[27] The cost utility studies[22,23,24] and the cost consequence analysis[27] were based on the results of randomised controlled trials both with sample sizes of 100 participants or more while the cost benefit analyses[25,26] were based on modelled data. All of the studies utilized oral nutritional supplements (ONS) as their intervention, although Norman et al.[23] also provided dietary counselling to their intervention and control groups. The participants were from different clinical groups with two studies focusing on patients with gastrointestinal disease,[23,26] two with older adults admitted to hospital,[22,27] one with older adults in residential care facilities,[24] and one in community dwelling older adults.[25] The studies also differed in the costs they included in their analysis. Norman et al.[23] only included the incremental cost of the intervention in their analysis, excluding any wider effect on the health system, while most other studies took a wider view point including costs of medical treatment and social care in the community.[22,25,27] There was a great variety in outcomes measured as listed in Table 2. The cost utility analysis by Norman et al.[23] found that providing 3 months of ONS to malnourished patients with benign gastrointestinal disease was associated with between €9497-12099 per quality-adjusted life year (QALY) gained. Although in Australia no explicit guideline for determining the cost effectiveness of new healthcare technologies has been provided, the Pharmaceutical Advisory Committee appears to consider interventions with cost per QALY below $50,000 as cost effective, and this intervention is well within this threshold indicating relatively high cost effectiveness.[28] Neelemat et al.[22] neared the cost-effectiveness threshold in their CUA providing ONS to older people admitted to hospital as well as routine Vitamin D and Calcium supplementation and telephone support from a Dietitian upon discharge. The results indicated a cost per QALY gain of €26962 for the intervention group compared to the controls. Cost benefit studies conducted by Freijer et al. in the Netherlands indicated cost savings of over €200 per patient in abdominal surgery patients receiving 2 cartons of ONS per day during their hospitalisation through a reduced length of stay,[26] and reported total budget savings of over

€12 million for the provision of ONS for treatment of malnutrition in community dwelling older people.[25] Pham et al.[24] found provision of ONS for the treatment of pressure ulcers in malnourished patients of residential care facilities was not cost effective in isolation, but argued that nutrition may play a wider role in supporting other prevention strategies beyond the scope of the economic model developed for their analysis. The remaining study was conducted in a community dwelling sample of older people over a 6 to 12 month follow up period and failed to demonstrate any cost savings for an 8 week intervention in a population of elderly and already malnourished subjects.[27] In summary therefore although the available economic evidence is scant, the studies which have been undertaken to date do demonstrate the potential for protein and energy supplementation in patients identified as malnourished to provide cost savings to the health system in addition to improved health outcomes for patients.

**Results of studies where nutritional status not specified**

Table 3 presents the results of studies including an intervention to improve nutritional status in a group of participants where their nutritional status was not specified.[29-38] Although relatively more studies were identified in this category, the studies were very diverse in terms of setting, interventions, and outcomes measured, making any direct comparisons across studies very difficult. In terms of study design, a range of designs were employed including randomised designs,[29-31,35] a number of non or quasi-randomised designs[32,33,36,37] and modelled studies.[34,38] Although sample size varied from less than 100 to over 2000, half of the studies included between 100 and 300 participants. Of the identified studies only one utilized a cost-utility approach.[29] This study assessed a multidisciplinary intervention including exercise and smoking cessation counselling in addition to ONS in community dwelling adults with chronic obstructive pulmonary disease and was found to be near the cost effectiveness threshold at AUD$39,438 per QALY gained (Table 3). Four of the studies utilized a cost-effectiveness analysis and reported upon a diverse range of outcome indicators including cost per one day reduction in length of stay, cost per kilocalorie consumed, or cost per kg of weight gained.[30-33] Findings ranged from cost of US$0.01 per kilocalorie additional consumed to cost of €76.10 per one day reduction in length of stay. Although Dangour et al.[30] found an ICER of US$4.84 per additional meter walked by their intervention group in a timed walking test, they only included the costs for the physical activity intervention not the nutrition intervention in their estimates, which could lead to an underestimate. All of these included ONS, aiming to provide between 1068kJ and 10g protein and to 2500kJ and 28g protein additional per day. Other interventions utilized included mid meal snacks, or fortified foods and five studies included a multifaceted intervention (two of which included an exercise or multidisciplinary intervention, and three which included routine early screening for nutritional status and issues). The studies also focused on different clinical groups such as patients from residential care homes,[31,37] patients with COPD discharged to the community,[29] community dwelling older adults,[30] and a large number focusing on patients from various hospital wards.[32-36,38] Follow up period was similarly varied across the studies ranging from the duration of hospital stay to a two year period, with the greatest proportion of studies (five out of nine) centred on the period of hospitalisation. In addition, the costs included in the analysis varied from the incremental costs of providing the intervention only,[30-32] compared to wider viewpoints including the costs of providing the intervention and medical treatment over the follow up time period.[29,33-37] One study focused on the changes in hospitalisation costs only.[38] Overall, while the heterogeneity of the studies makes synthesis of the outcomes difficult, they have generally indicated beneficial outcomes for the patient or health system, at a relatively low cost.

**Quality of Studies**

Overall when assessing the quality of the published studies, according to the widely recognised Drummond criteria the quality ranges greatly between studies, (Figure 2). Studies were of varying quality, with the number of 'yes' responses to the criteria ranging from a minimum of three to maximum of 27. Generally, the studies scored well on question 1 ("the research question is stated"), 5 ("the alternatives being compared are clearly described"), 22 ("time horizon of costs and benefits is stated"), and 32 ("conclusions follow from the data reported"). Questions completed less well included 14 ("productivity changes if included are reported separately"), 15 ("the relevance of productivity changes to the study question is discussed"), 23 ("the discount rate is stated"), and 24 ("the choice of rate is specified").

The paper which had the highest number of 'yes' responses to the criteria (n=28) was Pham et al.,[24] a recently published CUA of ONS in Residential Care patients closely followed by Norman et al.[23] (n=27) a cost utility study of ONS in malnourished patients with benign disease. This study found that ONS was cost effective. In general, it was found that the more recently published Cost Utility[22,23,29] and Cost Effectiveness studies[30-33] were of a higher quality than older published studies in terms of their adherence to the Drummond criteria. A few studies included only a partial report of healthcare costs such as general practitioner or health service visits.[27,37,38] However, these studies fail to provide a direct comparison between the costs and benefits provided by the interventions, and they therefore fail to take into consideration the value for money of the interventions from an economic perspective.[39]

**DISCUSSION**

In a comprehensive review of the published literature, sixteen papers were identified which included analysis of providing protein and energy supplementation for prevention or treatment of malnutrition from an economic view point. Of these, only four studies[22,23,24,29] utilised cost-utility analysis, which is currently recommended as the preferred method of economic evaluation for new health care interventions by the Pharmaceutical Benefits Advisory Committee and Medical Services Advisory Committee in Australia, and the National Institute for Health and Clinical Excellence in the UK as well as many other regulatory bodies around the world.[18-19]

Two of the cost-utility studies identified by the review concluded that the interventions under consideration (ONS for 3 months in patients with benign gastrointestinal disease who were also malnourished and ONS for 2 years in adults with Chronic obstructive pulmonary disease) were cost effective.[23,29] In both studies, the incremental cost per QALY ratios were below threshold values for determining cost effectiveness.[28] In another CUA, Neelemaat et al. 2012[22] neared the cost-effectiveness threshold for their intervention of ONS in malnourished hospitalised older adults, while Pham et al.[24] did not show cost effectiveness in prevention of pressure ulcers for in malnourished older people living in residential care facilities.

The studies identified in this review indicated an incremental cost of between -€392.00 to 478.20 (AUD$488.67- $596.12) for health outcomes such as a reduction in one day length of stay, additional metre walked, additional calories ingested, or per kg of weight gained.[30-38]. However, while these indicators appear broadly favourable, it is difficult to synthesise these outcomes due to their heterogeneous nature.[40] The utilization of the QALY, a generic measure of health outcome, for application within cost-utility analysis can be helpful in this regard in demonstrating the 'value for money' of nutrition therapy in a world of competition for scarce health budget resources.[40] The paucity of economic evidence has also been proposed as the main reason for the failure for uptake of national and international evidence based guidelines in the clinical setting.[40] Within this context, the lack of economic evaluations of protein and energy supplementation for malnutrition treatment coupled with the lack of utility-based outcomes for facilitating comparison across interventions and disease areas for decision-making is therefore a serious concern.

In addition, there were a small number of published studies targeted at the economic benefits of protein and energy supplementation to treat malnutrition in the older adult. However, this target group has received more attention recently, with three cost utility studies have been published recently within the last two years targeting the effectiveness of providing ONS to malnourished older people.[22,24,25] Of three cost effectiveness studies identified that targeted older participants, one failed to include the cost of the nutrition therapy itself in their estimation of cost effectiveness (which involved a physical function measure).[30] However, it is encouraging to see that there have been two randomised controlled trial protocols published since 2008 which include economic evaluation in their proposed evaluation of research into energy and protein supplementation as a treatment for or to prevent malnutrition.[41-42] These two studies are all focused on older adults and the study protocols all include consideration of costs of the intervention and associated health care utilisation (including costs of the nutrition intervention, specialist staff, hospital costs, community services, and medications) as well as non-medical costs (such as absenteeism and unpaid help) and health outcomes as such as QALYs, and functional status.

Many identified studies have a short follow up time of one year or less. This presents a challenge for clinicians aiming to demonstrate the benefits of nutrition support, as the short follow up time may not be long enough to allow the benefits to become apparent. When one study in community living elderly over a 6 to 12 month follow up period did not show cost savings in the intervention group compared to the control group, the authors hypothesised that their 8 week intervention was not sufficient to show improvement in their elderly and already malnourished population.[27] Also, the results of economic evaluations should be reported as an incremental cost effectiveness ratio (ICER) wherever possible. An ICER is important as it provides the decision-maker with the opportunity to determine the potential additional cost of a new health care intervention in order to achieve a given outcome. The use of a generic measure of health outcome such as the QALY in this context has the added advantage of facilitating comparisons of value for money across the health care system for example comparing investment in nutrition interventions for malnutrition in older people versus pharmacological treatments for dementia

In conclusion, to date few economic evaluations of protein and energy supplementation for treatment or prevention of malnutrition have been published and the quality of published studies is highly variable. However, the available economic evidence suggests that providing ONS of between 1068kJ and 10g protein up to 4200kJ and 23g protein is associated with positive economic benefits in both patients with malnutrition and in studies where nutritional status was not specified, and over short follow up times. Use of protein and energy supplementation in those with or at risk of malnutrition presents an opportunity for health services to reduce hospitalisation costs for a relatively small additional investment. In the absence of comprehensive economic evidence relating to its cost effectiveness, nutrition therapy is in danger of falling by the wayside in this new era of competitive health care funding. Future research should focus on the inclusion of high quality comprehensive economic evaluations alongside studies of clinical effectiveness to demonstrate the cost effectiveness of nutrition interventions for the treatment of malnutrition.

**CONFLICTS OF INTEREST**

The authors declare no conflict of interest

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**Conflict of Interest**

The authors declare no conflict of interest.

**Table 1.** Types of Economic Evaluation

| *Type of Evaluation* | *Abbreviation* | *Aim* | *Variables* | *Outcomes* | *Example* |
|---|---|---|---|---|---|
| Cost-utility analysis | CUA | Compares the costs associated with an intervention with a measure of utility which combines the life years gained by an intervention with a measure of the quality of those life years | Resource costs<br><br>Measure of utility (e.g. Quality Adjusted Life Year (QALY)) | Ratio of cost per QALY gained | Cost per QALY for a fish oil intervention which reduces joint pain in patients with arthritis. |
| Cost-effectiveness analysis | CEA | Compares the costs associated with an intervention with a measure of clinical effectiveness | Resource costs<br><br>Measure of clinical effectiveness | Cost per unit of clinical effectiveness | Cost of a unit reduction in blood cholesterol levels for a nutrition education intervention |
| Cost-consequence analysis | CCA | Compares the costs associated with an intervention with the consequences neither without combining these inputs nor without indicating the relative importance of the consequences. | Resource costs<br><br>Consequences | List of costs<br><br>List of possible outcomes<br><br>Up to the reader to make judgements about the benefits and drawbacks of the intervention | Cost of providing a nutrition education intervention, and a reported reduction in blood cholesterol levels in an intervention group, but without combining these outcomes into a ratio. |
| Cost –benefit analysis | CBA | Compares the benefits of the intervention in monetary terms with the costs of the intervention | Resource Costs<br><br>Benefits of the intervention in money | Net benefit of the intervention expressed in monetary terms | Commonly used for when a new treatment might involve an initial expenditure for treatment, but overall results in savings over time through reduce healthcare utilization. |

| | | | | | |
|---|---|---|---|---|---|
| Cost-minimisation analysis | CMA | Determine the least costly intervention where outcomes for two interventions are assumed to be equal | Resource costs | Difference in resource costs between two interventions | Measure the costs of providing hospital in the home program when the outcomes in morbidity, function, quality of life have been shown to be the same for as for inpatient care. |

**Table 2:** Design and cost outcomes of included studies when participants defined as malnourished

| *Citation* | *Design* | *Intervention* | *Population* | *n Subjects* | *Follow Up* | *Method* | *Sensitivity Analysis* | *Discounting* | *Unit* | *Cost per unit* | *Cost Intervention* | *Cost Comparison* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Neelemaat et al. 2012[22] | RCT | ONS (2520kJ and 24g protein) and malnutrition treatment protocol | Hospitalised older adults (Malnourished according to BMI or weight loss) | 210 | 3 months | CUA | Yes | N/A | Additional QALY | €26962<br>$US33703 | €9129 (1227)[1,2]<br>$US11411 (1534) | €8684 (1361)[1,2]<br>$US10855 (1701) |
| Norman et al. 2011[23] | RCT | ONS 3/12 (2505kJ and 23g protein) | Benign GI disease (Malnourished according to SGA) | 120<br>I=60<br>C=54 | 3 months | CUA | Yes | N/A | Additional QALY | €9497-12099<br>$US11904-15164 | €561 (514-609)[3,4]<br>$US703 (644-763) | €22 (0-73)[3,4]<br>$US28 (0-92) |
| Pham et al. 2011[24] | Model | ONS (1 carton per day, 8.4kJ/mL formula ) | Residential Care (Malnourished according to weight loss) | N/A | 3.8 years | CUA | Yes | Yes | Additional QALY | $CAN7824747<br>$US74306502 | - | - |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Freijer et al. 2012[25] | Model | ONS (2 cartons per day, NFS) | Community dwelling older people | 720223 | 1 year | CBA | Yes | N/A | Total budget savings | €12986000<br>$US16232500 | €262657000[5]<br>$US328321250 | €275643000[5]<br>$US344553750 |
| Freijer et al. 2010[26] | Model | ONS (2 cartons per day, NFS) | Abdominal surgery | N/A | Per admission | CBA | Yes | N/A | Mean cost of hospitalisation | -€252<br>$US316 | - | - |
| Edington et al. 2004[27] | RCT | ONS from hospital (2500 – 4200kJ) | Recently hospitalised older adults (Malnourished according to BMI or weight loss) | 100<br>I=51<br>C=49 | 6 months | CCA | No | N/A | - | - | £2989 (4418)[2,6]<br>$US4752 (7024) | £2146 (2238)[2,6]<br>$US3412 (3558) |

Abbreviations: BMI=Body Mass Index, C=Control, GI=Gastrointestinal, I=Intervention, N/A=Not applicable, NFS= Not further specified, ONS=Oral nutritional supplements, QALY=Quality adjusted life year, RCT=Randomised controlled trial, SGA=Subjective global assessment, 95%CI=95% Confidence intervals

1a Standard Error

2 Costs included for providing medical treatment and social services only

3 Costs included for providing intervention only

4 95% CI

5 Costs included for medical treatment and social services related to treatment of DRM

6 Standard Deviations

**Table 3:** Design and cost outcomes of included studies where nutritional status not specified

| *Citation* | *Design* | *Intervention* | *Population* | *n Subjects* | *Follow Up* | *Method* | *Sensitivity Analysis* | *Discount* | *Unit* | *Cost per Unit* | *Cost Intervention* | *Cost Comparison* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hoogendoorn et al. 2010[29] | RCT | ONS 4/12 (2351kJ and 28g protein) plus multi-disciplinary intervention | COPD | 199 I=102 C=97 | 2 years | CUA | Yes | No | Additional QALY | €32425 $US40400 | €13565[1] $US16901 | €10814[1] $US13474 |
| Dangour et al. 2011[30] | Randomised factorial trial | ONS (1068kJ and 10g protein) and/or physical activity | Community-dwelling older adults | 1669 ONS = 414, ONS+PA=452 PA=403 C[d]=400 | 2 years | CEA | Yes | Yes | Additional meter walked in 6 minute walking test | $US4.84[2] | Nutrition intervention $US91[3] | - |
| Simmons et al. 2010[31] | RCT | Snacks or ONS (NFS) | Residential Care | 63 ONS=18 Snacks=24 C=19 | 6 weeks | CEA | Yes | N/A | Additional kCal consumed | $US0.01 | ONS $US2.13 (0.37)[3,4] | - |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kruizenga et al. 2005[32] | Historical controlled trial | Malnutrition treatment protocol including high energy and protein meals (2500kJ and 12g protein additional) | Mixed ward patients | 588 I=297 (HEHP =98) C[d]=291 | Per admission | CEA | Yes | N/A | Mean cost per 1 days reduction in LOS (96%CI) | €35 (-1239-109) $US44 (-1544-136) | €37 (15-58)[3,5] $US46 (19-73) | - |
| Rypkema et al. 2003 [33] | Quasi-randomised controlled trial | Malnutrition protocol including treatment with high energy diet or ONS (NFS) | Geriatric ward patients | 298 I=140 C = 158 | Per admission | CEA | Yes | N/A | Kg gained | -€392 -$US489 | €7516[6] $US9366 | €7908[6] $US9854 |
| Russell 2007[34] | Model | ONS (NFS) | Surgical patients | N/A | Per admission | CBA | N/A | N/A | Mean difference in cost of hospitalisation intervention vs control | -£849 -$US1340 | - | - |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Smedley et al. 2004[35] | RCT | ONS (6.3kJ and 0.05g protein per ml drink ad libitum) before and after surgery (SS group) vs ONS before (SC group) vs ONS after (CS group) vs control (CC group) | Surgical patients | 152<br>CC=44<br>SS=32<br>CS=35<br>SC=41 | Up to 96 days | CBA | Yes | N/A | Mean difference in cost of hospitalisation intervention vs control | -£300<br>-$US473 | SS £2289 (2034-2717)[4,6]<br>$US3612<br>(3209-4287) | £2618<br>(2272-3181)[4,6]<br>$US4131 (3585-5019) |
| Lawson et al. 2003[36] | Prospective controlled trial | ONS (2500kJ and 20g protein) | Emergency and elective orthopaedic surgery | 181<br>I=84<br>C=97 | Per admission | CBA | No | N/A | Mean difference in cost of hospitalisation intervention vs control | -£16<br>-$US25 | £2069[6]<br>$US3264 | £2199[6]<br>$US3470 |
| Lorefält et al. 2011[37] | Non-randomised controlled trial | Malnutrition protocol including high energy high protein meal | Residential Care | 109<br>I=42<br>C=37 | 1 year | CCA | No | N/A | - | - | €1005[6]<br>$US1253 | €921[6]<br>$US1148 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | options (NFS) for 3 months | | | | | | | | | | |
| Tucker and Miguel 1996[38] | Model | ONS (NFS) | Hospital patients | 2485 | Per admission | CCA | N/A | N/A | Mean difference in cost of hospitalisation per year intervention vs control | -$US8294 | - | - |

Abbreviations: C=Control, COPD=Chronic obstructive pulmonary disease, GI=Gastrointestinal, HEHP=High energy high protein diet, I=Intervention, LOS=Length of stay, N/A=Not applicable, NFS=Not further specified, ONS=Oral nutritional supplements, PA=Physical activity, QALY=Quality adjusted life year,

1 Costs included for providing intervention plus medical treatment and loss of income for participant

2 Costs included for providing physical activity intervention only

3 Costs included for providing intervention only

4 Standard deviations

5 95% Confidence intervals

6 Costs included for providing intervention and medical treatment

**Legend for Figure 1.** Flow diagram of study selection process

**Legend for Figure 2.** Results of the quality analysis of the study designs.

Bars indicate the number of studies for which the quality criteria was met (black bar), not met (white bar), or not applicable for this study (grey bar). Quality criteria taken from the 35 item checklist by Drummond et al.[14] Quality criteria divided into items referring to study design (A), data collection (B), and analysis and interpretation of the results (C). Criteria questions are as follows: Q1, the research question is stated; Q2, the economic importance of the research is stated; Q3, the viewpoint(s) of the analysis are clearly stated and justified; Q4, the rationale for choosing the alternative programmes or interventions compared is stated; Q5, the alternatives being compared are clearly described; Q6, the form of economic evaluation used is stated; Q7, the choice of form of economic evaluation is justified in relation to the questions addressed; Q8, the source(s) of effectiveness estimates used are stated; Q9, details of the design and results of the effectiveness study are given (if based on a single study); Q10, details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies); Q11, the primary outcome measure(s) for the economic evaluation are clearly stated; Q12, methods to value health states and other benefits are stated; Q13, details of the subjects from whom valuations were obtained are given; Q14, productivity changes (if included) are reported separately; Q15, the relevance of productivity changes to the study question is discussed; Q16, quantities of resources are reported separately from their unit costs; Q17, methods for the estimation of quantities and unit costs are described; Q18, currency and price data are recorded; Q19, details of currency of price adjustments for inflation or currency conversion are given; Q20, details of any model used are given; Q21, the choice of model used and the key parameters on which it is based are justified; Q22, time horizon of costs and benefits is stated; Q23, the discount rate(s) is stated; Q24, the discount rate(s) is justified; Q25, an explanation is given if costs or benefits are not discounted; Q26, details of statistical tests and confidence intervals are given for stochastic data; Q27, the approach to sensitivity analysis is given; Q28, the choice of variables for sensitivity analysis is justified; Q29, the ranges over which the variables are varied are stated; Q30, relevant alternatives are compared; Q31 incremental analysis is reported; Q32, major outcomes are presented in a disaggregated as well as aggregated form; Q33, the answer to the study question is given; Q34, conclusions follow form the data reported; Q35, conclusions are accompanied by the appropriate caveats.

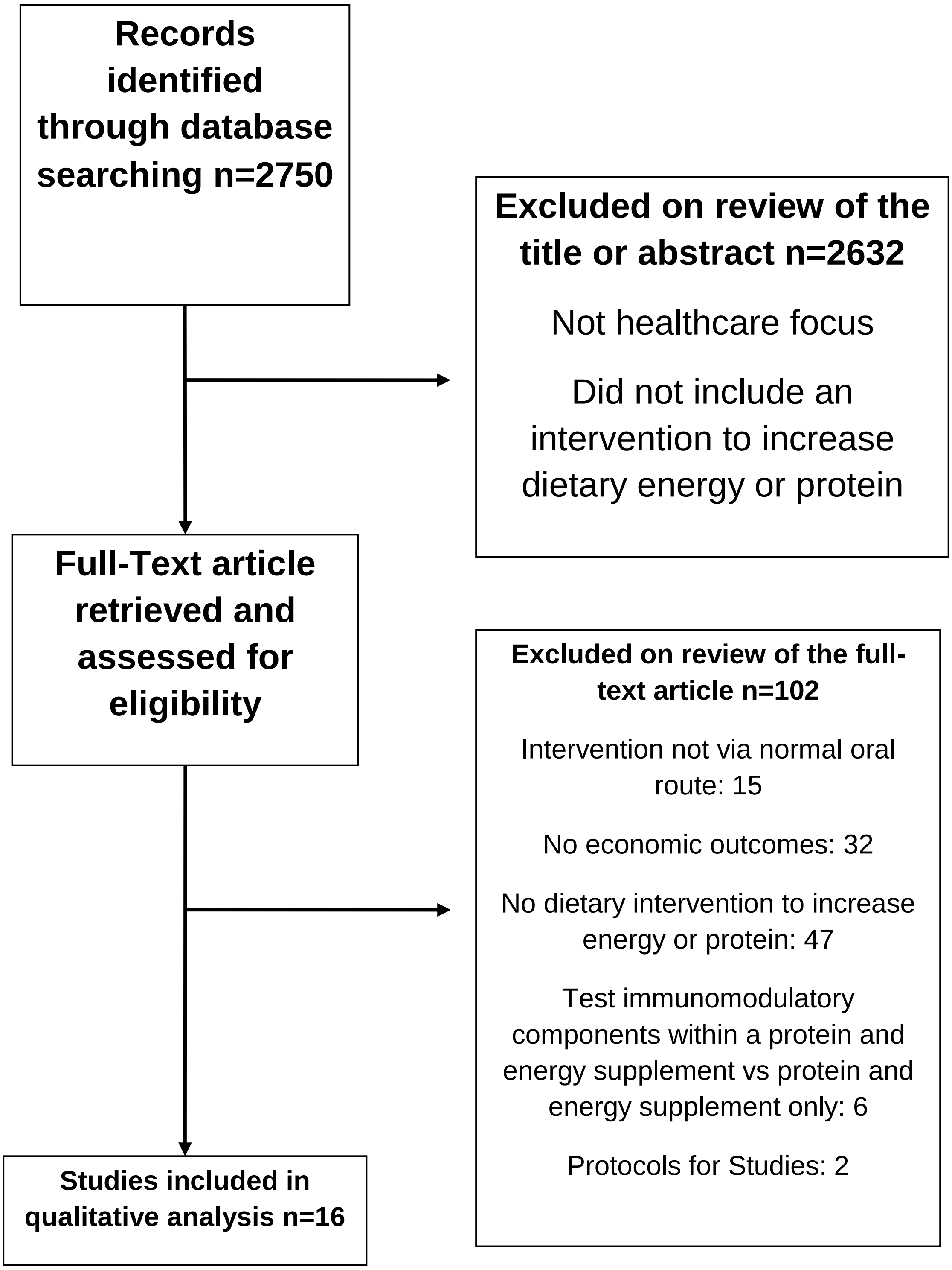


**Figure 1.** Flow diagram of study selection process

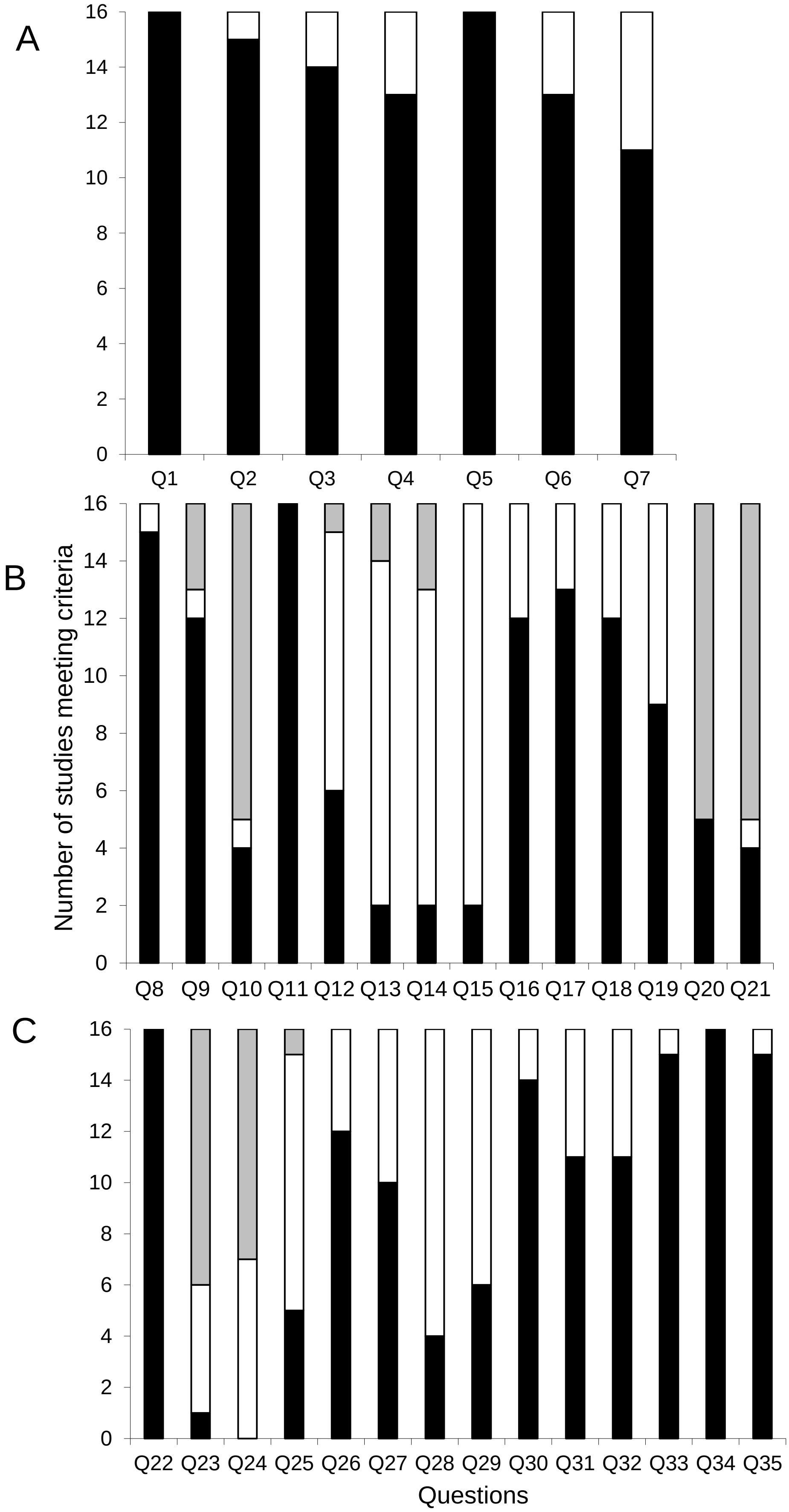
A
B
C
Number of studies meeting criteria
0
2
4
6
8
10
12
14
16
Q1
Q2
Q3
Q4
Q5
Q6
Q7
Q8
Q9
Q10
Q11
Q12
Q13
Q14
Q15
Q16
Q17
Q18
Q19
Q20
Q21
Q22
Q23
Q24
Q25
Q26
Q27
Q28
Q29
Q30
Q31
Q32
Q33
Q34
Q35
Questions

**Figure 2.** Results of the quality analysis of the study designs