Health economic analyses in medical nutrition: 
a systematic literature review

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Background: Medical nutrition is a specific nutrition category either covering specific dietary needs and/or nutrient deficiency in patients or feeding patients unable to eat normally. Medical nutrition is regulated by a specific bill in Europe and in the US, with specific legislation and guidelines, and is provided to patients with special nutritional needs and indications for nutrition support. Therefore, medical nutrition products are delivered by medical prescription and supervised by health care professionals. Although these products have existed for more than 2 decades, health economic evidence of medical nutrition interventions is scarce. This research assesses the current published health economic evidence for medical nutrition by performing a systematic literature review related to health economic analysis of medical nutrition.

Methods: A systematic literature search was done using standard literature databases, including PubMed, the Health Technology Assessment Database, and the National Health Service Economic Evaluation Database. Additionally, a free web-based search was conducted using the same search terms utilized in the systematic database search. The clinical background and basis of the analysis, health economic design, and results were extracted from the papers finally selected. The Drummond checklist was used to validate the quality of health economic modeling studies and the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist was used for published systematic reviews.

Results: Fifty-three papers were identified and obtained via PubMed, or directly via journal webpages for further assessment. Thirty-two papers were finally included in a thorough data extraction procedure, including those identified by a “gray literature search” utilizing the Google search engine and cross-reference searches. Results regarding content of the studies showed that malnutrition was the underlying clinical condition in most cases (32%). In addition, gastrointestinal disorders (eg, surgery, cancer) were often analyzed. In terms of settings, 56% of papers covered inpatients, whereas 14 papers (44%) captured outpatients, including patients in community centers. Interestingly, in comparison with the papers identified overall, very few health economic models were found. Most of the articles were modeling analyses and economic trials in different design settings. Overall, only eight health economic models were published and were validated applying the Drummond checklist. In summary, most of the models included were carried out to quite a high standard, although some areas were identified for further improvement. Of the two systematic health economic reviews identified, one achieved the highest quality score when applying the AMSTAR checklist.

Conclusion: The reasons for finding only a few modeling studies but quite a large number of clinical trials with health economic endpoints, might be different. Until recently, health economics has not been required for reimbursement or coverage decisions concerning medical nutrition interventions. Further, there might be specifics of medical nutrition which might not
allow easy modeling and consequently explain the limited uptake so far. The health economic data on medical nutrition generated and published is quite ample. However, it has been primarily based on database analysis and clinical studies. Only a few modeling analyses have been carried out, indicating a need for further research to understand the specifics of medical nutrition and their applicability for health economic modeling.

**Keywords:** systematic review, medical nutrition, health economics

### Introduction

Medical nutrition is a specific nutrition category either covering specific dietary needs and/or nutrient deficiencies in patients or providing nourishment for patients who are unable to eat normally. Medical nutrition is available in different formulations and consistencies, providing energy, protein, fluid, electrolyte, mineral, micronutrient, and fiber needs. It depends on activity levels and the underlying clinical condition, for example, catabolism, pyrexia, gastrointestinal tolerance, potential metabolic instability, risk of refeeding problems, and likely duration of nutrition support, among others. There are different options available for the administration of nutrition support, including oral, enteral, and parenteral formulations, by application of special devices like infusions, tubes, probes, or perfusions. Use of medical nutrition needs skilled health care professionals who are trained in nutritional requirements and methods of nutrition support to ensure that the treatment support given provides a suitable nutrient intake for patients.

Medical nutrition is regulated by a specific bill in both Europe and in the US, with specific legislation and guidelines, and is provided for patients with specific nutritional needs and indications for nutrition support. Therefore, like prescription pharmaceuticals, medical nutrition products are delivered on medical prescription under the supervision of health care professionals.

Although these products have existed for more than 2 decades, the health economic evidence of medical nutrition interventions tends to be scarce. In the field of health technology research, including phar-macoconomics, health economics research is usually described according to its methods, including cost-effectiveness analysis, cost-utility analysis, and budget impact analyses. In addition, in health economics, research concepts concerning the financial burden of disease are widely used to highlight the financial implications of a disease from the societal perspective at a regional or national level.

To get a better understanding of medical nutrition-related health economics and to advance the greater picture of application of health economics in medical nutrition, this systematic literature review was undertaken to assess the current evidence.

### Methods

The research question of particular interest was formulated as: “What is the evidence of health economics in medical nutrition, what concepts are applied, and what is their quality?”

The research question was defined in more detail applying the PICO (population [P], intervention [I], comparison [C], and outcome(s) [O]) criteria to conduct a literature review most suitable to answer the research question (see Table 1).

A systematic literature search was initiated and performed based on a predefined search protocol. Before a final set of search terms was defined, a pilot search was conducted to assess the relevant terms to be included. The following search terms were used at the pilot stage:

- “health economics”, “cost of illness”, “cost minimization”, “cost(s)”, “cost-effectiveness”, “cost utility”, “budget impact”
- “medical nutrition”, “medical food”, “FSMP”, “EN”, “nutritional support/supplement”.

Finally, some preliminary considerations were made regarding feasibility and in order to not compromise the results. Hence, it was validated that the same results could be gained when using the term “cost” with different wordings as a search term, eg, in comparison with “costs”, “cost of illness”, “cost minimization”, cost-effectiveness”, “cost utility”, and “cost benefit”. Consequently, the term “economic assessment” was taken out because this was also captured under the term “health technology assessment”; the same was true for the term “cost(s)” because this was captured by all cost papers with the other terms. Additionally, the term “health economics” was not considered because it was seen that only health policy papers turned out. Relevant papers which would have shown up under these terms were also captured by the other search terms used. Finally, it was decided to take out the term “oral nutrition supplement” because this was shown to be covered by the term “nutritional(al) supplement”. Final search terms were identified accordingly:

- terms “a” for medical nutrition included economics: a1) economic evaluation; a2) health technology assessment; a3) cost effectiveness; a4) cost of illness; a5) cost minimization; a6) cost benefit; a7) cost utility; a8) budget impact

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**Table 1**

| Search Term(s) | Relevant Papers |
|---------------|-----------------|
| a1             | 110             |
| a2             | 10              |
| a3             | 54              |
| a4             | 32              |
| a5             | 74              |
| a6             | 90              |
| a7             | 97              |
| a8             | 147             |

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**Note:** Numbers refer to the number of relevant papers identified under each term.
• terms “b” for medical nutrition were defined as follows: b1) medical food; b2) medical nutrition; b3) nutritional support; b4) nutrition supplement; b5) enteral nutrition; b6) food for special medical purpose; b7) FSMP.

Terms covered with “a” were then combined with all terms “b” during the actual systematic literature search. In order to narrow the search to more relevant articles, only papers published between 2000 and 2012 and in the Dutch, English, French, German, Italian, or Spanish language were included in the final review process.

Full-text publications were obtained for abstracts that met the predefined inclusion criteria. Abstracts that did not meet the search criteria were excluded. Based on these full-text reports, it was decided whether each study met the selection criteria. The area of interest was therefore defined as: only articles with content related to food for special medical purpose (EU terminology [FSMP]) or medical food (US terminology), known as medical nutrition in an oral or enteral format. Further, this search was solely focused on health economic data in the context of medical nutrition, so only papers with an explicit health economic content, verified by the common methods applied, met the selection criteria and were assessed further. Publications without a health economic component/analysis were excluded.

The relevant data in the identified papers were captured on a data extraction sheet. All health economic (modeling) studies identified were assessed for quality using the Drummond checklist. Further, all reviews identified were assessed using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist. Further, all reviews identified were assessed using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist.

Results
A first run of the systematic literature search was done in PubMed using a search strategy with sequenced search loops whereby each term could be searched individually (see Figure 1). Utilization of the connected terms by Boolean operator were utilized and a second run (for “true” findings) was run. For the terms “FSMP”, “food for special medical purpose”, and “enteral nutrition”, it was felt not to be meaningful to use the same Boolean operators due to the already limited number of findings. Hence, it seemed to be more useful to connect the latter term with another Boolean operator, ie, “NOT”. The results for any economic term in combination with “FSMP” or with “food for special medical purpose” appeared as “0”. The only exception, ie, “food for special medical purpose” AND “economic evaluation”, yielded an output of “1”. In total, 38 articles were identified using this process and were subjected to further investigation. In a third search sequence, each economic term was searched in combination with nutritional terms. In total, 419 articles were identified for further investigation, including those of the first two search loops.

Another search within the National Health Service Economic Evaluation Database was conducted specifically for the economic term “economic evaluation” in combination with all “nutritional” terms. This was appropriate given that this database is a repository only for economic evaluations. For this search, 75 articles were retrieved for further investigation.

A search of the Health Technology Assessment Database was done only for the economic term “health technology assessment” in combination with all nutritional terms. This was considered appropriate because this database is a repository only for health technology assessments. Used in addition to the term “enteral nutrition”, no other nutrition search term provided any result. Twenty articles were identified for further investigation.

Within the fourth and final search loop for the 553 papers identified, the abstracts were analyzed for individual search terms and checked for alternative wording and variations within the context. Papers that included health economic data in conjunction with medical nutrition(s) were included in the further assessment. Within this final step, all duplications were identified. In total, 328 articles were excluded. A total of 225 abstracts were identified for the detailed review and the data were inserted into a data extraction sheet.

Within this narrative scrutiny of the data, all articles with a focus on primary prevention were excluded, as well as all articles solely focusing on clinical data without a health economic component/analysis. For the abstracts that finally met the predefined inclusion criteria, the abstracts were assessed for quality using the Drummond checklist. Further, all reviews identified were assessed using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist.

Clinical basis for evaluation and setting
When checking the clinical basis, it appeared that malnutrition was the underlying disease covered in most papers. In addition, gastrointestinal disorders (eg, surgery, cancer) were often included. More importantly, a rather large mix of different diseases were the subject of various studies, so
it is rather difficult to determine a trend except for the two categories just mentioned.

However, reviewing the results of the identified studies (see Figure 2), it became apparent that the majority of studies included interventions using enteral nutrition and oral nutritional support (seven and nine, respectively) with standard of care and parenteral nutrition as the comparator (ten and six, respectively).

In terms of settings, 63% of papers (20 studies) covered inpatients whereas 41% of papers (14 studies) captured outpatients, including patients in community centers. When analyzing the countries where the studies were conducted, most of the papers were from the US and UK (seven studies each, together comprising 44% of all studies included). The Netherlands and Italy followed, with five and four papers, respectively, even though in both countries the same groups of researchers dominated those papers (Nuijten et al in the Netherlands and Braga et al in Italy). Most other countries had only one paper, with the exception of Germany, which had three.

**Specific indications**
In order to draw indication and disease-specific conclusions, the results were divided into the following areas: malnutrition, gastrointestinal surgery, cow milk protein allergy (CMPA), and others.

**Malnutrition**
Of the extracted papers, roughly one third (eleven papers, 34%) covered the indication of malnutrition.
the papers identified covered the indication of malnutrition related to patients in developed countries only, as opposed to the common definition of malnutrition in developing countries. Of the eleven studies identified, five included hospitalized patients only, two included outpatients only, and three papers stated that community-based patients were included. Most of those papers considered more than one health economic endpoint. Six studies evaluated a form of cost analyses (eg, total cost, physician cost, prescription cost), and three had cost-effectiveness (or cost-utility) analyses defined as an endpoint. Budget impact and length of stay were each the subject of two papers. The economic results reported introduction of oral nutritional support as being cost-effective, even though the incremental cost-effectiveness ratios ranged significantly between studies. Interestingly, even though the introduction of oral nutritional support in comparison with a standard of care approach normally generates higher costs (and more efficacy), it was shown by different authors to be cost-saving from a budget impact perspective.

Gastrointestinal surgery
The second most studied indication identified was gastrointestinal surgery (nine studies, 28%). One paper was a systematic review, and the remaining eight had a direct hospital perspective. One paper had a national perspective, although also covering the hospital setting. All papers including the total cost of treatment as well as the cost of potential complications concluded that medical nutrition was superior in terms of cost over any comparator. Budget impact analyses showed similar results. In a few studies, cost-effectiveness results were also presented, and were also in favor of oral nutritional support. However, these results need to be interpreted with caution because no incremental cost-effectiveness ratios were calculated or provided.

Cow milk protein allergy
Another disease area, primarily analyzed by one research group led by Guest (see Table 2, studies 25–30) was CMPA. All studies were based in the community health care setting. In each of the studies, a decision model was used, including specific country input data, although the base case clinical and economic data were provided from a real-life UK database. Studies for the UK, Finland, Australia, the Netherlands, and South Africa descriptively analyzed the budget impact and cost situation for the health care systems, newly introducing a treatment for patients with CMPA. Cost-effectiveness or cost-comparison analyses were missing. In conclusion, the authors reported the current cost of managing those patients. Further, in some countries, they showed that inclusion of clinical nutrition in the reimbursement schemes would result in cost savings due to lower follow-up costs.

Other indications
In addition to the three most analyzed disease areas, some studies covered the following areas: pancreatitis, eating problems, dysphagia, and critically ill patients. For pancreatitis, two different studies were performed and both showed that enteral feeding was cost-saving in comparison with parenteral feeding. Such a cost-saving has also been found in critically ill patients. An analysis of patients with advanced dementia and eating problems showed that support with feeding tubes was cost-saving. For dysphagia, administration of enteral feeding tube was compared to normal diet while delivered at home versus nursing home. The analysis demonstrated that enteral tube feeding is cost-effective compared to no intervention independent of the setting.

Modeling approaches
In comparison with the articles identified overall, only a very few health economic model analyses were found. Overall, eleven models (34% of all studies extracted) were published, of which only eight could be considered health economic models and could be validated applying the Drummond checklist within this survey (see Table S1). The others usually did not describe their cost and modeling approach and therefore could not be fully identified as health economic models. Most of the papers that included health economic outcomes in medical nutrition were studies using different methods, eg, randomized controlled trials, observational trials, or cluster studies. Thirteen studies were identified, corresponding to 38% of all identified papers. Other designs included reviews, database analyses, and population-based models. All details of the selected papers can be seen in Table 2.
| Reference     | Disease area and classification | Health care setting | Intervention                                                                                     | Model design       | Setting and perspective | Health economic reporting (endpoints)                      |
|---------------|--------------------------------|---------------------|--------------------------------------------------------------------------------------------------|--------------------|-------------------------|----------------------------------------------------------|
| Abou-Assi et al⁶ | Acute pancreatitis            | Hospital            | Initial 48-hour intravenous fluids and analgesics. After patients improved, they were restarted on oral feeding. The remaining patients were randomized to a nasojejunal group (EN) or parenteral group (TPN) | Randomized clinical trial in one center | Hospital perspective in the US | Average cost for hospitalization; length of stay; average cost per stay; nutritional costs |
| Freijer and Nuijten⁷ | Abdominal surgery, GI surgery | Hospital            | ONS versus no ONS                                                                                 | Cost-effectiveness model | National perspective | Hospitalization costs; length of stay; societal budget impact |
| Gianotti et al⁸  | Surgery in GI cancer patients, GI surgery | Hospital            | Perioperative administration of enteral IN or standard enteral diet                               | Calculation based on RCT and cost data | Hospital perspective | Cost of nutrition; cost of complications; cost-effectiveness |
| Kruizenga et al⁹ | Malnourished hospitalized patients with different diseases | Hospital            | Intervention group: patients admitted to two mixed medical and surgical wards and received both malnutrition screening at admission and standardized nutritional care (tube feeding and parenteral feeding). Control group received the usual hospital clinical care | Controlled trial with a historical control group | Societal perspective | Length of stay; cost-effectiveness |
| Neelemaat et al¹⁰ | Malnourished hospitalized patients (newly admitted to the wards of general internal medicine, rheumatology, gastroenterology, dermatology, nephrology, orthopedics, traumatology, and vascular surgery) | Hospital            | Intervention group: nutritional supplementation (energy and protein enriched diet, oral nutritional support, calcium + vitamin D supplementation, telephone counseling by a dietician) until 3 months after discharge from hospital. Patients in the control group received usual care (control) | RCT in one center | Societal perspective (one hospital center) | Cost-effectiveness; cost-utility; detailed direct health care cost; indirect cost |
| Norman et al¹¹  | Patients with a benign GI-related malnutrition Malnutrition | Hospital            | Either ONS for 3 months and dietary counseling at discharge (intervention) or only dietary counseling at discharge (control group) | Pilot RCT           | One center in Germany | Cost-effectiveness; cost-utility |

Table 2 Detailed overview of papers identified with respect to key study items

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| Name            | Malnourished condition | Setting     | Intervention                                                                 | Study Type       | Perspective | Cost Components                                                                 |
|-----------------|------------------------|-------------|-------------------------------------------------------------------------------|------------------|-------------|---------------------------------------------------------------------------------|
| Wilson et al    | Malnourished hemodialysis patients | Outpatient | Oral supplementation early in the course of malnourished hemodialysis patients | Pilot RCT        | Hemodialysis centers in the US | Length of stay |
| Mitchell et al  | Advanced dementia      | Nursing home residents | ETF versus hand-feeding by nurse | Retrospective cohort study | Long-term care facility in the US | Daily costs of nursing home care; detailed cost overview of items covered and not covered by Medicaid |
| Freijer et al   | Disease-related malnutrition | Community | ONS (intervention) versus no ONS | Budget impact     | National perspective | Budget impact |
| Elia and Stratton | Cerebrovascular accident | Outpatient | ETF in nursing home versus at home | Cost-utility model | Not reported | Cost-utility |
| Louie et al     | Acute pancreatitis     | Hospital    | PN versus EN                                                                   | RCT              | Health authority in Canada | Average total cost; cost for radiology; cost for intensive care; operative costs |
| Smedley et al   | Lower GI surgery       | Hospital    | Oral supplements (Fortisip®, Nutricia, Rockville, MD, USA) both before and after surgery. Randomization to the following groups: no nutritional supplements, supplements both before and after surgery, postoperative supplements only, supplements only before surgery | Two-phase, RCT   | Hospital perspective | Mean overall costs |
| Edington et al  | Patients after discharge from hospital | Outpatient | Elderly malnourished subjects were randomized to 8 weeks of supplementation (Ensure Plus®, Tetrapak, Enlive® Tetrpak, Formance®, Ensure Pudding or Bars, Abbott Laboratories, Abbott Park, IL, USA) or no supplementation post-discharge, and followed up for 24 weeks | Multicenter, prospective open-label, RCT | NHS perspective | Quality of life; cost of prescription; cost of consultation; cost of appointment; cost of hospital admission; cost of hospital (stay) |
| Strickland et al | Well-nourished surgical patients | Hospital | Immune-modulating formulations could be either: Impact® (Novartis Nutrition Corporation, Minneapolis, MN, USA) or Immun-Aid® (B Braun, Irvine, CA, USA) | Database analysis | US hospital for patients covered by Medicare or Medicaid Services | Cost of complications; length of stay |
| Reference          | Disease area and classification | Health care setting | Intervention | Model design | Setting and perspective | Health economic reporting (endpoints) |
|--------------------|---------------------------------|---------------------|--------------|--------------|-------------------------|---------------------------------------|
| Braga et al²       | Cancer of the stomach, pancreas, or esophagus GI surgery | Hospital            | Randomization into two groups receiving postoperative TPN or early EN | Prospective, RCT | Department of surgery in an Italian university hospital | Mean cost per day; cost of prescription |
| Braga and Gianotto | Gastrointestinal cancer GI surgery | Hospital            | Preoperative group receiving oral Impact for 5 days before surgery; perioperative group receiving the same preoperative treatment plus jejunal infusion of impact for 7 days after surgery; and a conventional group | Clinical study | Hospital perspective | Total cost; cost of inpatient routine care; cost of complications; cost-effectiveness |
| Braga and Rocchetti | Gastrointestinal cancer GI surgery | Hospital            | Preoperative immunonutrition versus no nutritional support | Review | Not available | Cost of nutrition; cost of complications; cost-effectiveness |
| Braga et al²       | Gastrointestinal cancer GI surgery | Hospital            | Oral preoperative specialized diet versus conventional treatment (no supplementation) | Prospective, RCT | Italian university hospital | Cost of postoperative complications; costs per complication; cost per randomized patient |
| Cangelosi et al²³  | Critically ill patients          | Hospital (ICU)      | PN or EN | Systematic review and cost analysis | Not available | Length of stay; budget impact |
| Nuijten and Mittendorf | Patients with risk of disease-related malnutrition Malnutrition | Hospital            | ONS versus no ONS | Linear decision analytic model | Not reported | Total cost; cost of hospitalization |
| Arnaud-Battandier et al²⁴ | Malnutrition patients Malnutrition | Community           | Two groups of physicians were selected based on historical prescribing practice: group 1 with rare and group 2 with frequent prescription of oral nutrition supplements (only oral high energy high protein nutritional supplement that has a pharmaceutical status on the French market) | Observational, prospective, longitudinal, cohort study | Community/physician perspective | Cost of hospital care; cost of nursing care; cost of other medical care; costs related to nutritional products; total cost |
| Mauskopf et al²⁵   | Gastrointestinal cancer GI surgery | Hospital            | Oral or enteral dietary supplementation with arginine, omega-3 fatty acids, and nucleotides (known as IN) Comparator: IN perioperative (EN or ONS) versus standard of care | Database analysis | Hospital perspective | Total cost; cost of infectious complication rates; cost on length of hospital stay |
| Author(s) | Disease-related Malnutrition | Setting | Oral Nutritional Supplements | Study Design | Cost Review | Annual Expenditure on Disease-related Malnutrition Patients | Cost of Healthcare Resources (GP Consultations; Hospitalization); Total Cost | Total Cost per Patient; Budget Impact |
|-----------|-----------------------------|---------|-----------------------------|-------------|------------|--------------------------------------------------------|-------------------------------------------------|----------------------------------|
| Russell   | Disease-related malnutrition Malnutrition | Hospital and community setting | Oral nutritional supplements ONS (no comparator) | Cost review | Hospital and community perspective | Annual expenditure on disease-related malnutrition patients; cost of hospital care; cost of supplements | Health care resources (GP consultations; hospitalization); total cost | Total cost per patient; budget impact |
| Guest et al | Malnutrition patients Malnutrition | Community | Disease-specific medical nutrition Comparators and treatments not specified | Database matched analysis | Community/physician perspective | Community | Community | Community | Community |
| Sladkevicius et al | CMPA | Community | Treatment data and hence split of patient groups according to UK market data | Computer-based budget impact model | Community | Community | Community | Community | Community |
| Guest and Valovirta | CMPA | Community | Soy, eHF, Neocate® AAF (Nutricia) based on assumptions and literature | Decision budget impact model | KELA (health insurance), patient and society | Total expenditure on clinical nutrition preparations; acquisition cost of clinical nutrition preparations | 6-monthly health care cost | 6-monthly health care cost | 6-monthly health care cost |
| Guest and Nagy | CMPA | Community | Soy, eHF, AAF | Decision budget impact model | Publicly funded health care system | Cost of health care resource use; cost of clinical nutrition preparations; cost of clinician visits | Cost of health care resource use; cost of clinical nutrition preparations; cost of clinician visits | Cost of health care resource use; cost of clinical nutrition preparations; cost of clinician visits | Cost of health care resource use; cost of clinical nutrition preparations; cost of clinician visits |
| Sladkevicius and Guest | CMPA | Community | Soy, eHF, AAF | Decision budget impact model | Insurer, parents/carer | Annual cost for insurer, parents/carer; budget impact | Annual NHS cost | Annual NHS cost | Annual NHS cost |
| Taylor et al | CMPA | Community | eHF versus AAF | Decision model | Community | Community | Community | Community | Community |
| Ockenga et al | Malnutrition patients in a gastroenterology ward Malnutrition | Inpatients Nutritional support (including oral supplements, parenteral feeding, parenteral tube feeding) Comparison: ONS, EN, and PN | G-DRG relevant variables were prospectively collected | Hospital | Direct cost for nutritional support | Hospital | Direct cost for nutritional support | Hospital | Direct cost for nutritional support |
| Mutch et al | Pancreatitis | Inpatients EN versus PN support Comparison: EN versus PN | Retrospective review of pre-existing database | Hospital in the US | Total cost | Hospital in the US | Total cost | Hospital in the US | Total cost |

**Abbreviations:** AAF, amino-acid formulas; CMPA, cow milk allergy; En, enteral nutrition; ICU, intensive care unit; IN, immunonutrition; NHS, National Health Service; ONS, oral nutritional supplements; ETF, enteral tube-feeding; G-DRG, German diagnosis-related groups; GI, gastrointestinal; PN, parenteral nutrition; RCT, randomized controlled trial; TPN, total parenteral nutrition; eHF, extensively hydrolyzed; KELA, Kansaneläketaitos, Social Insurance Institution Finland; GP, general practitioner.
For all the health economic modeling papers selected, a study quality assessment was conducted using the Drummond checklist (for details, see Table S1). Overall, the included models were implemented with a high standard of quality, even though some areas were identified for further improvement (e.g., sensitivity analysis and databases). Further, in the papers reported by Guest and Nagy in 2009 and Guest et al in 2011, the main weaknesses were poor reporting of the underlying and used effectiveness basis in the models.

Two systematic reviews on health economic studies in medical nutrition were found during the literature search process, and the AMSTAR checklist was used to assess them. Of these reviews, the one by Cangelosi et al achieved the highest quality scores applying the AMSTAR checklist (for details, see Table S2). Most questions could be answered, and the paper included all relevant information. An important difference between this review and the one published by Braga and Rocchetti in 2011 was that Cangelosi et al also searched the gray literature and reported both included and excluded studies.

Discussion
A couple of cost-effectiveness, cost comparison, and budget impact analyses were published in recent years. However, most of the cost-effectiveness (cost utility) analyses normally being published were based on health economic models and not actually run semi-clinical studies with a health economic endpoint as it was shown in the retrieved evidence for medical nutrition. As this systematic literature search has shown, potential reasons for such a difference might be that there is not only interest in health economics and its application in medical nutrition, but also some activities ongoing, increasingly adopting the use of health economic modeling. Further burdens compared with the established pharmaceutical and medical device regulations might include differences in terms of reimbursement and market access requirements for medical nutrition products. This seems especially true given that cost-effectiveness analyses were mainly associated with drug and medical device reimbursement decisions, where, in many countries, financial considerations of affordability may be as important as clinical efficacy and cost-effectiveness.

Conclusion
The health economic data on medical nutrition generated and published is quite ample. However, they have been primarily based on database analysis and clinical studies. Few modeling analyses have been carried out, indicating a need for further research to understand the specifics of medical nutrition and their applicability in health economic modeling.

Disclosure
This study was funded by Nestlé Health Science. The authors have no other conflicts of interest in this work.

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**Supplementary materials**

**Table S1 Quality assessment of health economic modeling studies according to the Drummond checklist**

| Item | Freijer et al | Freijer and Nuijten | Nuijten and Mittendorf |
|------|--------------|----------------------|-----------------------|
| 1. Was a well defined question posed in answerable form? | Yes | Yes | Yes |
| a. Did the study examine both costs and effects of the service(s) or program(s)? | Yes (incremental approach: for effects only (re) hospitalizations were taken into account) | Yes | Yes |
| b. Did the study involve a comparison of alternatives? | No | No | No |
| c. Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context? | Yes | Yes | No |
| 2. Was a comprehensive description of the competing alternatives given (ie, can you tell who did what to whom, where, and how often)? | No | No | No (not expected) |
| a. Were there any important alternatives omitted? | Yes (was performed) | Yes (was performed) | Yes (was performed) |
| b. Was (should) a do-nothing alternative be considered? | Yes | Yes | Yes |
| 3. Was the effectiveness of the program or services established? | Yes (based on published literature) | Yes (based on published literature) | Yes (based on published literature) |
| a. Was this done through a randomized, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice? | Yes (even though not stated if done in a systematic manner) | No |
| b. Was effectiveness established through an overview of clinical studies? | Yes (all assumptions were conservative) | No |
| c. Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results? | Yes | Yes | Yes |
| 4. Were all the important and relevant costs and consequences for each alternative identified? | No | No | No |
| a. Was the range wide enough for the research question at hand? | Yes | Yes | Yes |
| b. Did it cover all relevant viewpoints (possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis)? | Yes (relevant viewpoint for a budget impact analysis is the national health care payer view which was used) | No (decided viewpoint was that of the society) | No (only one viewpoint was taken into account even though not defined) |
| c. Were the capital costs, as well as operating costs, included? | Yes | Yes | Yes |
| 5. Were costs and consequences measured accurately in appropriate physical units (eg, hours of nursing time, number of physician visits, lost work days, gained life years)? | No items omitted | No items omitted | No items omitted |
| a. Were any of the identified items omitted from measurement? If so, do this mean that they carried no weight in the subsequent analysis? | Yes (rationale was given in the article) | Yes (rationale was given in the article) | Yes (rationale was given in the article) |
| b. Were there any special circumstances (eg, joint use of resources) that made measurement difficult? | Yes (rationale was given in the article) | Yes (rationale was given in the article) | Yes (rationale was given in the article) |
| 6. Were the cost and consequences valued credibly? | Yes | Yes | Yes |
| a. Were the sources of all values clearly identified (possible sources include market values, patient or client preferences and views, policymakers’ views and health professionals’ judgments)? | Yes | Yes | Yes |
| Sladkevicius et al<sup>a</sup> | Guest et al<sup>b</sup> | Guest and Nagy<sup>c</sup> (UK) | Sladkevicius and Guest<sup>d</sup> (the Netherlands) | Sladkevicius and Guest<sup>e</sup> (South Africa) |
|-------------------------------|-----------------------------|--------------------------------|--------------------------------------------------|-----------------------------------------------|
| Yes                           | Yes                         | Yes                            | Yes                                              | Yes                                           |
| Yes                           | Yes                         | Yes                            | Yes                                              | Yes                                           |
| Yes                           | Yes                         | Yes                            | Yes                                              | Yes                                           |
| No                            | No                          | No                             | No                                               | No                                            |
| No                            | No                          | No                             | No                                               | No                                            |
| Yes                           | No                          | No                             | Yes                                              | Yes                                           |
| No (GP database analysis as basis) | No                      | No                             | No (UK database and interviews)                  | No (UK database)                              |
| No                            | No                          | No                             | No                                               | No                                            |
| Yes (biases mentioned in article) | Yes                      | Yes                            | Yes (biases mentioned in article)                | Yes (biases mentioned in article)             |
| Yes                           | Yes                         | Yes                            | Yes                                              | Yes                                           |
| Yes                           | Yes                         | Yes                            | Yes                                              | Yes                                           |
| No                            | Yes                         | Yes                            | No                                               | No                                            |
| No                            | No                          | No                             | No                                               | No                                            |
| Yes                           | Yes                         | Yes                            | Yes                                              | Yes                                           |
| No item omitted               | No item omitted             | No item omitted                | No item omitted                                  | No item omitted                               |
| Yes                           | Yes                         | Yes                            | Yes                                              | Yes                                           |
| Yes                           | Yes                         | Yes                            | Yes                                              | Yes                                           |
| Yes                           | Yes                         | Yes                            | Yes                                              | Yes                                           |

(Continued)
**Table S1 (Continued)**

|   | Freijer et al⁴ | Freijer and Nuijten² | Nuijten and Mittendorf² |
|---|-----------------|----------------------|------------------------|
| b. Were market values employed for changes involving resources gained or depleted? | Yes | Yes | Yes |
| c. Where market values were absent (eg, volunteer labor), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values? | Not applicable | Not applicable | Not applicable |
| d. Was the valuation of consequences appropriate for the question posed (ie, has the appropriate type or types of analysis [cost-effectiveness, cost-benefit, cost-utility] been selected)? | Yes | Yes | Yes |

7. **Were costs and consequences adjusted for differential timing?**

|   | Freijer et al⁴ | Freijer and Nuijten² | Nuijten and Mittendorf² |
|---|-----------------|----------------------|------------------------|
| a. Were costs and consequences that occur in the future “discounted” to their present values? | No (as time horizon was below 1 year) | No (as time horizon was below 1 year) | No |
| b. Was there any justification given for the discount rate used? | Yes | No | No |

8. **Was an incremental analysis of costs and consequences of alternatives performed?**

|   | Freijer et al⁴ | Freijer and Nuijten² | Nuijten and Mittendorf² |
|---|-----------------|----------------------|------------------------|
| a. Were the additional (incremental) costs generated by one alternative over another compared with the additional effects, benefits, or utilities generated? | Yes | Yes | Yes |

9. **Was allowance made for uncertainty in the estimates of costs and consequences?**

|   | Freijer et al⁴ | Freijer and Nuijten² | Nuijten and Mittendorf² |
|---|-----------------|----------------------|------------------------|
| a. If data on costs and consequences were stochastic (randomly determined sequence of observations), were appropriate statistical analyses performed? | No (not applicable as difficult to perform based on published data only) | No (not applicable as difficult to perform based on published data only) | No |
| b. If a sensitivity analysis was employed, was justification provided for the range of values (or for key study parameters)? | Yes | Yes | Yes |
| c. Were the study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)? | Yes (reasonable changes to be expected) | Yes (reasonable changes to be expected) | Yes |

10. **Did the presentation and discussion of study results include all issues of concern to users?**

|   | Freijer et al⁴ | Freijer and Nuijten² | Nuijten and Mittendorf² |
|---|-----------------|----------------------|------------------------|
| a. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (eg, cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion? | Yes (budget impact results interpreted in the context and including sensitivity analysis) | Yes (quantitative and qualitative interpretation of ICER) | Yes |
| b. Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology? | Yes (no alternative publication available) | Yes | Yes |
| c. Did the study discuss the generalizability of the results to other settings and patient/client groups? | No | No | No |
| d. Did the study allude to, or take account of, other important factors in the choice or decision under consideration (eg, distribution of costs and consequences, or relevant ethical issues)? | No | No | No |
| e. Did the study discuss issues of implementation, such as the feasibility of adopting the “preferred” program given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programs? | Yes | Yes | Yes |
| Sladkevicius et al<sup>4</sup> | Guest et al<sup>1</sup> | Guest and Nagy<sup>4</sup> (UK) | Sladkevicius and Guest<sup>7</sup> (the Netherlands) | Sladkevicius and Guest<sup>4</sup> (South Africa) |
|----------------------------|---------------------|-------------------------------|-----------------------------------------------|-----------------------------------------------|
| Yes                        | Yes                 | Yes                           | Yes                                           | Yes                                           |
| Not applicable             | Not applicable      | Yes                           | Not applicable                                | Not applicable                                |
| No (12-month analysis)     | No (6-month analysis) | No (6-month analysis)         | No (12-month analysis)                        | No (12-month analysis)                        |
| No                         | No                  | No                            | No                                            | No                                            |
| Not applicable             | Not applicable      | Not applicable                | Not applicable                                | Not applicable                                |
| No                         | No                  | No                            | No                                            | No                                            |
| Yes                        | Yes                 | Yes                           | Yes                                           | Yes                                           |
| No                         | No                  | No                            | No                                            | No                                            |
| No                         | No                  | No                            | No                                            | No                                            |
| Yes                        | Yes                 | Yes                           | Yes                                           | Yes                                           |
| No (only GP visit as changing parameter) | Yes | Yes | No (only GP visit as changing parameter) | No (only GP visit as changing parameter) |
| Yes                        | Yes                 | Yes                           | Yes                                           | Yes                                           |
| Yes (budget impact results interpreted in the context and including sensitivity analysis) | Yes | Yes | Yes (budget impact results interpreted in the context and including sensitivity analysis) | Yes (budget impact results interpreted in the context and including sensitivity analysis) |
| Yes                        | Yes                 | Yes                           | Yes                                           | Yes                                           |
| Yes                        | Yes                 | Yes                           | Yes                                           | Yes                                           |
| No                         | No                  | No                            | No                                            | No                                            |
| Yes                        | Yes                 | Yes                           | Yes                                           | Yes                                           |
| No                         | No                  | No                            | No                                            | No                                            |
| Yes                        | Yes                 | Yes                           | Yes                                           | Yes                                           |
| Abbreviations: GP, general practice; ICER, incremental cost-effectiveness ratio; ONS, oral nutritional supplements. |
Table S2  Health economic review quality assessment applying the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist

|   | Cangelosi et al1 | Braga and Rocchetti10 |
|---|----------------|-----------------------|
| 1. Was an “a priori” design provided? | Yes | Yes |
| 2. Was there duplicate study selection and data extraction? | Yes | No |
| 3. Was a comprehensive literature search performed? | Yes | Yes |
| 4. Was the status of publication (ie, gray literature) used as an inclusion criterion? | Yes | No |
| 5. Was a list of studies (included and excluded) provided? | Yes | No |
| 6. Were the characteristics of the included studies provided? | Yes | Yes |
| 7. Was the scientific quality of the included studies assessed and documented? | Yes | No |
| 8. Was the scientific quality of the included studies used appropriately in formulating inclusions? | Yes | No |
| 9. Were the methods used to combine the findings of studies appropriate? | Yes | Yes |
| 10. Was the likelihood of publication bias assessed? | No | No |
| 11. Was the conflict of interest included? | Yes | No |

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