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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

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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 pharmacoeconomics, 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[1] 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 "nutrition(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

- 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 recent 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.[2] Further, all reviews identified were assessed using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist.[3]

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, full-text publications were obtained.

Fifty-three articles were identified and obtained via PubMed, or directly via the journal webpage for further assessment. After a detailed review of the full-text papers, 32 publications were included in a thorough data extraction procedure, including those identified by a "gray literature search" utilizing the Google search engine and cross-reference searches.

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

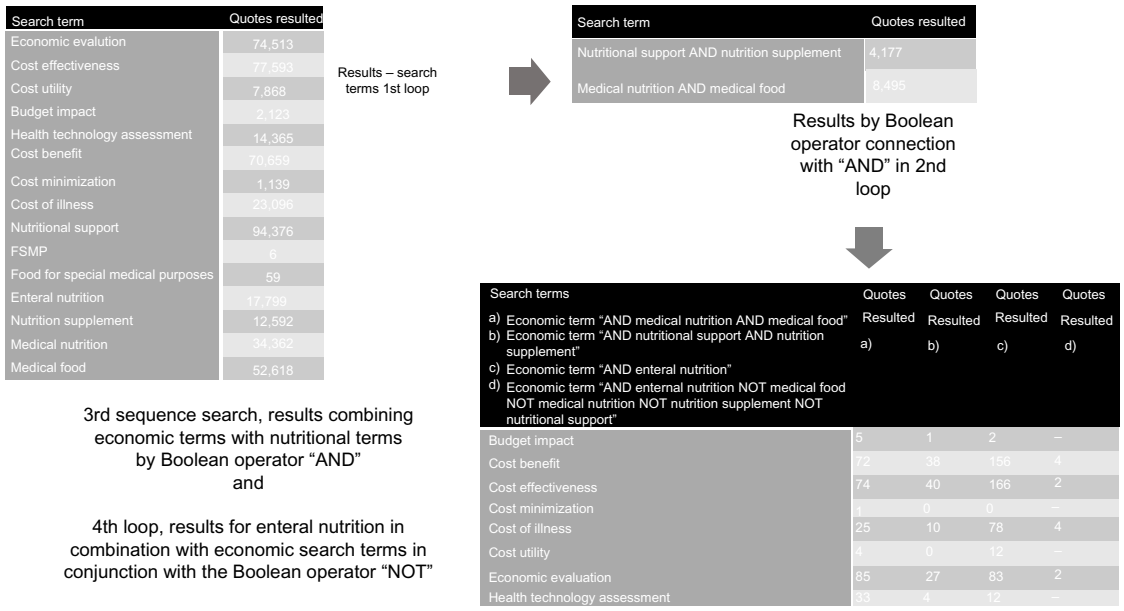

Figure 1 Process and findings of the systematic literature search for health economics in medical nutrition.
Abbreviation: FSMP, food for special medical purpose.

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[4] in the Netherlands and Braga et al[5] 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. Prerequisite, according to the particular interest of this survey,

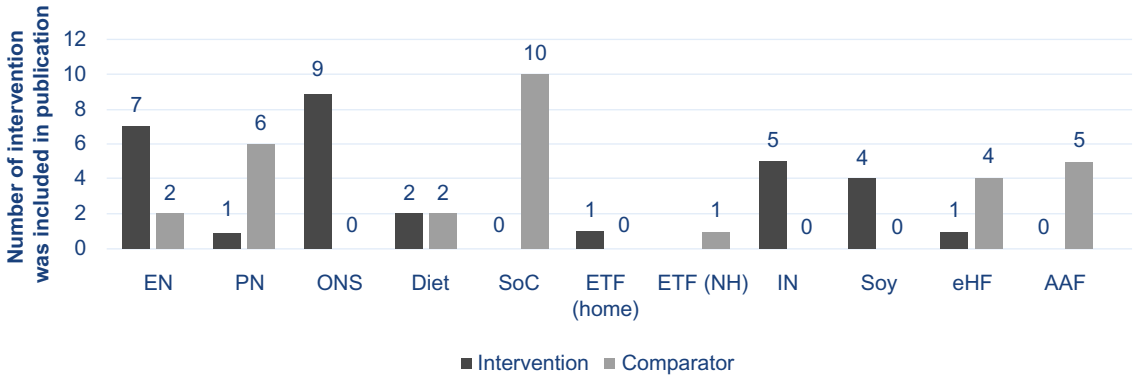

Figure 2 Interventions and comparators included in the health economic analyses identified by a systematic literature search.
Abbreviations: AAF, amino acid formula; EN, enteral nutrition; ETF, enteral tube-feeding; eHF, extensively hydrolyzed; NH, nursing home; IN, immunonutrition; ONS, oral nutritional supplements; PN, parenteral nutrition; SoC, standard of care.

Table 1 PICO criteria for the systematic literature search

PICO criteria	Definition
Patient and Intervention	Medical nutrition/oral or enteral formulas, FSMP, medical food, ONS, oral nutrition, enteral nutrition, total enteral nutrition, nutrition/nutritional intervention, support, supplements, formulas
Comparison	Patients with versus without medical nutritionals/FSMP/medical food/ONS/parenteral nutrition or total parenteral nutrition; potentially secondary prevention
Outcomes	Cost(s), cost-effectiveness, cost per QALY, cost-saving, cost of illness, cost minimization, health economics; willingness to pay; (re)hospitalization; morbidity and mortality; complications; utility

Abbreviations: FSMP, food for special medical purpose; ONS, oral nutrition supplements; QALY, quality-adjusted life year; PICO, population, intervention, comparison, and outcome(s).

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.

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

Reference	Disease area and classification	Health care setting	Intervention	Model design	Setting and perspective	Health economic reporting (endpoints)
Abou-Assi et al[6]	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) Comparison: EN versus 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 Nuijten[7]	Abdominal surgery, GI surgery	Hospital	ONS versus no ONS Comparison: ONS versus no ONS	Cost-effectiveness model	National perspective	Hospitalization costs; length of stay; societal budget impact
Gianotti et al[8]	Surgery in GI cancer patients, GI surgery	Hospital	Perioperative administration of enteral IN or standard enteral diet Comparison: ONS + enteral IN versus standard of care	Calculation based on RCT and cost data	Hospital perspective	Cost of nutrition; cost of complications; cost-effectiveness
Kruizenga et al[9]	Malnourished hospitalized patients with different diseases Malnutrition	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 Comparison: EN versus PN	Controlled trial with a historical control group	Societal perspective	Length of stay; cost-effectiveness
Neelemaat et al[10]	Malnourished hospitalized patients (newly admitted to the wards of general internal medicine, rheumatology, gastroenterology, dermatology, nephrology, orthopedics, traumatology, and vascular surgery) Malnutrition	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) Comparison: ONS into diet protocol versus standard of care	RCT in one center	Societal perspective (one hospital center)	Cost-effectiveness; cost-utility; detailed direct health care cost; indirect cost
Norman et al[11]	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) Comparison: ONS + dietary counseling versus dietary counseling	Pilot RCT	One center in Germany	Cost-effectiveness; cost-utility

Wilson et al[12]	Malnourished hemodialysis patients Malnutrition	Outpatient	Oral supplementation early in the course of malnourished hemodialysis patients Comparison: ONS in mild versus ONS in moderate/severe hemodialysis patients	Pilot RCT	Hemodialysis centers in the US	Length of stay
Mitchell et al[13]	Advanced dementia Eating problems	Nursing home residents	ETF versus hand-feeding by nurse Comparison: ETF versus standard of care (including normal food intake with nursing help)	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[14]	Disease-related malnutrition Malnutrition	Community	ONS (intervention) versus no ONS Comparison: ONS versus no ONS	Budget impact	National perspective	Budget impact
Elia and Stratton[15]	Cerebrovascular accident Dysphagia	Outpatient	ETF in nursing home versus at home Comparison: ETF in different health care settings: home versus nursing home	Cost-utility model	Not reported	Cost-utility
Louie et al[16]	Acute pancreatitis	Hospital	PN versus EN Comparison: PN versus EN	RCT	Health authority in Canada	Average total cost; cost for radiology; cost for intensive care; operative costs
Smedley et al[17]	Lower GI surgery 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 Comparison: ONS versus ± ONS before/after surgery	Two-phase, RCT	Hospital perspective	Mean overall costs
Edington et al[18]	Patients after discharge from hospital Malnutrition	Outpatient	Elderly malnourished subjects were randomized to 8 weeks of supplementation (Ensure Plus® Tetrapak, Enlive® Tetrapak, Formance®, Ensure Pudding or Bars, Abbott Laboratories, Abbott Park, IL, USA) or no supplementation post-discharge, and followed up for 24 weeks Comparison: ONS versus no ONS	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[19]	Well-nourished surgical patients Malnourished surgical patients Trauma patients Medical ICU patients GI surgical and ICU patients	Hospital Before/after surgery After trauma/ ICU admission	Immune-modulating formulations could be either: Impact® (Novartis Nutrition Corporation, Minneapolis, MN, USA) or Immun-Aid® (B Braun, Irvine, CA, USA) Comparison: ONS versus no ONS	Database analysis	US hospital for patients covered by Medicare or Medicaid Services	Cost of complications; length of stay

(*Continued*)

Table 2 (*Continued*)

Reference	Disease area and classification	Health care setting	Intervention	Model design	Setting and perspective	Health economic reporting (endpoints)
Braga et al[5]	Cancer of the stomach, pancreas, or esophagus GI surgery	Hospital	Randomization into two groups receiving postoperative TPN or early EN Comparison: EN versus PN	Prospective, RCT	Department of surgery in an Italian university hospital	Mean cost per day; cost of prescription
Braga and Gianotti[20]	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 Comparison: IN oral or enteral versus standard of care in preoperative or perioperative regimen	Clinical study	Hospital perspective	Total cost; cost of inhospital routine care; cost of complication; cost-effectiveness
Braga and Rocchetti[21]	Gastrointestinal cancer GI surgery	Hospital	Preoperative immunonutrition versus no nutritional support Comparison: preoperative IN (oral) versus no ONS support	Review	Not available	Cost of nutrition; cost of complications; cost-effectiveness
Braga et al[22]	Gastrointestinal cancer GI surgery	Hospital	Oral preoperative specialized diet versus conventional treatment (no supplementation) Comparison: preoperative IN (oral) versus no ONS support	Prospective, RCT	Italian university hospital	Cost of postoperative complications; costs per complication; cost per randomized patient
Cangelosi et al[23]	Critically ill patients	Hospital (ICU)	PN or EN Comparison: EN versus PN	Systematic review and cost analysis	Not available	Length of stay; budget impact
Nuijten and Mittendorf[4]	Patients with risk of disease-related malnutrition Malnutrition	Hospital	ONS versus no ONS Comparison: ONS versus no ONS	Linear decision analytic model	Not reported	Total cost; cost of hospitalization
Arnaud-Battandier et al[24]	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) Comparison: ONS versus no ONS	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 al[25]	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

Russell[26]	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
Guest et al[27]	Malnutrition patients Malnutrition	Community	Disease-specific medical nutrition Comparators and treatments not specified	Database matched analysis	Community/ physician perspective	Health care resources (GP consultations; hospitalization); total cost
Sladkevicius et al[28]	CMPA	Community	Treatment data and hence split of patient groups according to UK market data	Computer-based budget impact model	Community	Total cost per patient; budget impact
Guest and Valovirta[29]	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
Guest and Nagy[30]	CMPA	Community	Soy, eHF, AAF	Decision budget impact model	Publicly funded health care system	6-monthly health care cost
Sladkevicius and Guest[31]	CMPA	Community	Soy, eHF, AAF	Decision budget impact model	Health care insurers	Cost of health care resource use; cost of clinical nutrition preparations; cost of clinician visits
Sladkevicius and Guest[32]	CMPA	Community	Soy, eHF, AAF	Decision budget impact model	Insurer, parents/carer	Annual cost for insurer, parents/carer; budget impact
Taylor et al[33]	CMPA	Community	eHF versus AAF	Decision model	Community	Annual NHS cost
Ockenga et al[34]	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
Mutch et al[35]	Pancreatitis	Inpatients	EN versus PN support Comparison: EN versus PN	Retrospective review of pre-existing database	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, Kansaneläkelaitos, 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 quite a high standard of quality, even though some areas were identified for further improvement (eg, sensitivity analysis and databases). Further, in the papers reported by Guest and Nagy[30] in 2009 and Guest et al[27] in 2011, the main weaknesses was 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[23] 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[21] in 2011 was that Canegelosi 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.[36]

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

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Supplementary materials

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

	Freijer et al[1]	Freijer and Nuijten[2]	Nuijten and Mittendorf[3]
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 Only reasonable comparison is "no ONS"	No Only reasonable comparison is "no ONS"	No Only reasonable comparison is "no ONS"
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)?	Yes	Yes	No
a. Were there any important alternatives omitted?	No	No	No (not expected)
b. Was (should) a do-nothing alternative be considered?	Yes (was performed)	Yes (was performed)	Yes (was performed)
3. Was the effectiveness of the program or services established?	Yes	Yes	Yes
a. Was this done through a randomized, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?	Yes (based on published literature)	Yes (based on published literature)	Yes (based on published literature)
b. Was effectiveness established through an overview of clinical studies?	Yes (even though not stated if done in a systematic manner)	Yes (even though not stated if done in a systematic manner)	No
c. Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?	Yes (all assumptions were conservative)	Yes (all assumptions were conservative)	No
4. Were all the important and relevant costs and consequences for each alternative identified?	Yes	Yes	Yes
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?	No An incremental comparison approach was being applied and was deemed as reasonable	No An incremental comparison approach was being applied and was deemed as reasonable	No An incremental comparison approach was being applied and was deemed as reasonable
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)?	Yes	Yes	Yes
a. Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?	No items omitted	No items omitted	No items omitted
b. Were there any special circumstances (eg, joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?	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[4]	Guest et al[5]	Guest and Nagy[6] (UK)	Sladkevicius and Guest[7] (the Netherlands)	Sladkevicius and Guest[8] (South Africa)
Yes	Yes	Yes	Yes	Yes
Yes	Yes	Yes	Yes	Yes
Yes	Yes	Yes	Yes	Yes
Yes	Yes	Yes	Yes	Yes
Yes	No	No	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 al[1]	Freijer and Nuijten[2]	Nuijten and Mittendorf[3]
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?	Yes (for cost)	Yes (for cost)	No (not reported)
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?	Yes	Yes	Yes
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?	Yes	Yes	Yes
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?	Yes	Yes	Yes
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[4]	Guest et al[5]	Guest and Nagy[6] (UK)	Sladkevicius and Guest[7] (the Netherlands)	Sladkevicius and Guest[8] (South Africa)
Yes	Yes	Yes	Yes	Yes
Not applicable	Not applicable	Yes	Not applicable	Not applicable
Yes	Yes	Yes	Yes	Yes
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
No	No	No	No	No
Yes	Yes	Yes	Yes	Yes
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

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 al[9]	Braga and Rocchetti[10]
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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8. Sladkevicius E, Guest JF. Modelling the health economic impact of managing cow milk allergy in South Africa. *J Med Econ*. 2010;13:257–272.
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