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Meta-analysis

The effect of post-discharge oral nutritional supplements on outcomes after gastrointestinal surgery: A systematic review and meta-analysis

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SUMMARY

Background: Malnutrition is a risk-factor for adverse postoperative outcomes. This systematic review and meta-analysis evaluated the impact of post-discharge oral nutritional supplements (ONS) on outcomes in patients undergoing gastrointestinal surgery.

Methods: The Medline and Embase databases were searched for randomised clinical trials in patients undergoing gastrointestinal surgery who had received ONS for at least two weeks after discharge from hospital. The primary endpoint was weight change. Secondary endpoints included quality of life, total lymphocyte count, total serum protein and serum albumin. Analysis was performed using RevMan5.4 software.

Results: Fourteen studies with 2480 participants (1249 ONS/1231 controls) were included. Pooling of results revealed that a reduction in postoperative weight loss in patients taking ONS, when compared with control: overall weighted mean difference (WMD) −1.69 kg, 95% CI −2.98 to −0.41, P = 0.01. Serum albumin concentration was increased in the ONS group: WMD = 1.06 g/L, 95% CI 0.04 to 2.07, P = 0.04. Haemoglobin was also increased: WMD = 2.91 g/L, 95% CI 0.58 to 5.25, P = 0.01. Total serum protein, total lymphocyte count, total cholesterol and quality of life did not differ between the groups. Patient compliance was relatively poor across the studies and there was variability in the composition of ONS, volume consumed and surgical procedures performed.

Conclusions: There was a reduction in postoperative weight loss and an improvement in some biochemical parameters in patients receiving ONS after gastrointestinal surgery. Future RCTs with more consistent methodologies are needed to investigate the efficacy of ONS after discharge from hospital following gastrointestinal surgery.

1. Introduction

Up to 45% of surgical patients are malnourished at admission [1] and of those who are malnourished, as few as 3% may be properly identified and diagnosed [2]. Malnourished patients are at risk of prolonged hospital length of stay, increased morbidity and mortality, higher healthcare costs [3–8], and a reduction in quality of life [9]. Patients undergoing gastrointestinal surgery are especially vulnerable to malnutrition, as many undergo procedures which affect the functionality of their digestive system. After gastrectomy, patients can experience increased satiety after smaller meals [10]. Patients undergoing oesophagectomy often have dysphagia and those undergoing colorectal surgery can experience reduced nutrient absorption. Nutrient digestion and absorption can be reduced after pancreatic surgery. The risk is heightened for patients with cancer due to cachexic processes, and for the frail and elderly who have reduced muscle mass [11].

The metabolic response to surgery instigates a variety of metabolic and endocrine changes and the perioperative catabolic response is characterised by a period of negative nitrogen balance

Abbreviations: BWL, body weight loss; CI, confidence intervals; EORTC, European Organisation for Research and Treatment of Cancer; ESPEN, European Society for Clinical Nutrition and Metabolism; NICE, National Institute for Health and Care Excellence; ONS, oral nutritional supplements; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT, randomised clinical trial; SI, International System; WMD, weighted mean difference.

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leading to increased muscle and fat breakdown, stimulation of the sympathetic nervous system and insulin resistance [12–14]. Increased metabolic activity leads to an increase in body temperature and respiratory rate: in patients undergoing elective surgery, there can be a 10–15% increase in basal energy expenditure [15] and if complications do not occur, it takes 3–8 days for a transition from catabolism to anabolism to occur [16]. It is, therefore, common for patients to experience weight loss following gastrointestinal surgery [17,18]. It has been found that 50% of patients lost over 10% of their body weight a year after upper gastrointestinal surgery [6] and half of patients undergoing colorectal surgery failed to reach their calorie intake target, with almost no patient reaching their protein intake target after discharge from hospital [19].

Oral nutritional supplements (ONS) can deliver a high concentration of macronutrients to patients. Currently, the National Institute for Health and Care Excellence (NICE) [20] and European Society for Clinical Nutrition and Metabolism (ESPEN) [18] guidance recommend preoperative and perioperative supplementation. However, evidence is confounding and unclear regarding the efficacy of post-discharge ONS. In comparison with perioperative measures, there is a lack of protocols regarding nutrition in the post-discharge period [18]. There are only two existing systematic reviews that evaluate ONS [21,22], but they do not include the most recent publications and are limited by both clinical and statistical heterogeneity. There is a disparity within the literature regarding when and who should use ONS: in one study, ONS was advocated in acutely ill and elderly populations. Other studies have found most benefit in patients with gastric cancer, and still others have deemed alternative, newer methods such as home enteral nutrition more effective than ONS [23]. Although malnutrition rates are significant across the inpatient population, 90% of cases actually occur in the community setting [24]. A study that measured adherence to ESPEN guidelines and associations with postoperative outcomes after surgery for upper gastrointestinal cancer showed there was poor adherence to most ESPEN guidelines and that nutritional inadequacy was associated with increased complications [25]. This underlines the need to explore the benefits of ONS in an outpatient context, especially as it has been established that maximum weight loss can occur up to 12 months after surgery [6].

Consequently, this systematic review and meta-analysis investigated the impact of ONS for a minimum of 14 days after discharge, on the outcomes after gastrointestinal surgery.

2. Methods

2.1. Search strategy

A comprehensive and systematic search of the Medline and EMBASE electronic databases from January 1980 to April 2022 was performed to identify all randomised clinical trials (RCTs) reporting on ONS administered for a minimum period of 14 days in the discharge period following gastrointestinal surgery.

The search terms for the intervention included [exp nutrition* supplement] OR [exp dietary supplement] OR [supplement*] mapped to corresponding Medline Subject Headings (MeSH). These were combined with the gastrointestinal operative procedures. The search was limited to human studies, and adult patients aged 18 years or older. The Scottish Intercollegiate Guidelines Network (SIGN) search filter was used to retrieve only RCTs. The comprehensive search was undertaken in October 2021 and the detailed strategy can be found in the Supplementary Document.

2.2. Article selection

The titles and abstracts of studies identified from the searches were screened for suitability, against the inclusion criteria independently by three study authors (AR, AA and AK). The remaining full-text articles were screened in detail independently by AR and AA and all discordance adjudicated by a third reviewer (DNL).

2.3. Eligibility of studies

Studies were included if they were RCTs, performed on adult human participants undergoing a gastrointestinal surgical procedure who received ONS following discharge from hospital for at least 14 days. All nutritional supplements were considered if they contained a source of increased calorie and or protein intake.

Studies in paediatric populations, those not reporting on ONS (including jejunostomy feeding), and studies where the nutritional supplements were provided only in the in-patient setting were excluded. Studies on animals, case reports, correspondence, comments, editorials and quasi-randomised trials were also excluded.

2.4. Outcome measures

The primary outcome measure was weight loss (kg and % body weight loss - BWL) from the time of discharge to the end of the study in the patient population. Secondary outcomes included reported serum biochemistry (including serum albumin, pre-albumin, C-reactive protein – CRP and total cholesterol), body composition, hand grip strength, costs, postoperative complications, patient compliance and quality of life. For secondary outcomes, the data used were taken as close to 90 days post-discharge as possible. However, all studies noted that there were no differences within the values in both the ONS and control groups at baseline.

2.5. Data extraction

Data were extracted by AR, AA and AK, with DNL adjudicating on any discordance. All the individual outcomes from each included study were recorded, and the quantitative data were extracted. Due to the different lengths of interventions across the studies, end point data were extracted as close to 90 days after the post-discharge intervention commenced. For weight loss (the primary outcome), the end point-data were compared with baseline data reported by the individual studies. Baseline data were taken preoperatively or at hospital admission. Meta-analyses were performed on the predetermined outcomes where appropriate.

2.6. Data analysis

Statistical analysis was performed using RevMan5.4.1 software [26]. All the outcomes of interest involved continuous data, so weighted mean difference (WMD) with 95% confidence intervals (CI) were used for reporting these outcomes. There was a variation in the units used throughout the studies. Consequently, for the purposes of meta-analysis, relevant values were converted into the International System (SI) of units. For outcomes with insufficient data availability only a narrative report of results is presented. Pooled data were analysed using the random-effects model with the inverse variance or Mantel-Haenszel method as appropriate. Statistical heterogeneity was assessed using the I^2 statistic with the following interpretation of values as outlined in the Cochrane Handbook [27].

- 0%–40% might not be important,
- 30%–60% may represent moderate heterogeneity,
- 50%–90% may represent substantial heterogeneity,
- 75%–100% considerable heterogeneity.

For studies that did not include the raw data values of outcomes, the WebPlotDigitser v4.6 (https://apps.automeris.io/wpd/) was used to obtain mean values. Unit conversion was implemented in cases where there was heterogeneity in units across data for a set outcome. If standard deviation values were not reported in the data, software approved in the Cochrane Handbook was used to calculate and estimate the standard deviation, where appropriate. For studies where data could not be appropriately obtained despite the aforementioned methods, data were presented as a narrative capacity and excluded from the meta-analysis. Differences between groups were considered significant at $P < 0.05$. Risk of bias in the included studies was assessed with the Cochrane Risk of Bias 2 (RoB2) tool [28].

2.7. Protocol registration

The protocol was registered with the PROSPERO database (registration number: CRD42020196375 https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=196375). The study was performed in accordance with the guidance of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [29].

3. Results

A total of 1756 studies were identified from our original database searches. After removal of duplicates and screening of titles and abstracts, 30 studies were considered eligible for full text review. However, as two studies were unobtainable full text screening for eligibility was carried out on 28 studies. One study [30] was excluded as it measured change in mass via dual-energy x-ray absorptiometry, which was not used in the other studies. Another study [31] was excluded due to the lack of published raw data available for the meta-analysis. Fourteen studies were included in this review [1,32–44] (Fig. 1).

3.1. Participants

These 14 studies included a total of 2480 participants whose results were analysed on an intention to treat basis: 1249 in the intervention arm and 1231 in the control group. In two of the studies, patients underwent oesophageal surgery [33,44], four studies involved partial/total gastrectomy [37,41–43], and two studies involved hepatic resection [36,38]. Three studies described surgical interventions as gastrointestinal surgery [1,35,40], and a further three studies involved procedures for patients with either gastric or colorectal cancer [32,34,39]. Further details are listed in Table 1.

3.2. Nutritional intervention and administration

There were eight different supplements used in the 14 studies. Four studies used Ensure (Ross Laboratories, UK), there were two studies that each used Nutren Optimum (Nestle Health Science, Vevey, Switzerland) and Aminoleban (Otsuka Pharmaceutical, Tokyo, Japan). The remaining studies used either Fortisp (Nutricia, Wageningen, The Netherlands), Anom (Otsuka Pharmaceutical, Japan), Elental (Ajinomoto Pharmaceuticals, Japan), Encover (EN Otsuka Pharmaceutical, Hanamaki City, Japan) or Racol (Otsuka Pharmaceuticals Factory, Tokyo, Japan). One study did not report the supplement used [33]. For

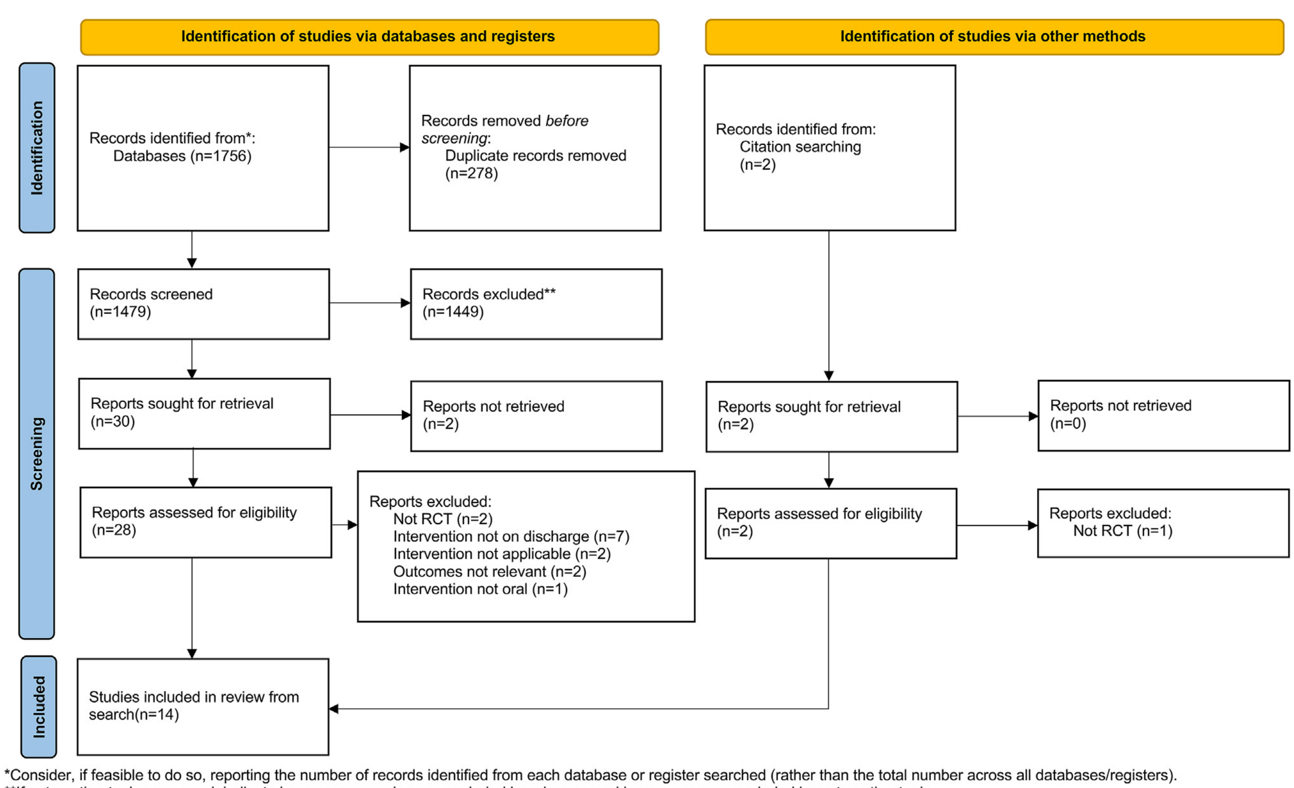

Fig. 1. PRISMA flow diagram of search and inclusion strategy.

Table 1
Characteristics of included studies.

Study, Year	No of participants	Type of surgery	Primary endpoint	Secondary endpoint	Source of Funding
Beattie 2000 [1]	101	Elective gastrointestinal or vascular	Weight change (compared with hospital admission) Anthropometry (TSF, MAMC) Grip strength	Complications Antibiotic use Quality of life (using SF-36 questionnaire)	Abott Laboratories
Chen [44]	60	Radical surgery for oesophageal malignancy (McKeown or Ivor-Lewis procedure)	BMI PG-SGA	Haemoglobin Serum albumin Serum prealbumin CD4 CD8 CD4/8 IgG IgA IgM	N/A
Hatao 2017 [43]	113	Elective total gastrectomy or distal gastrectomy	Post-operative percent weight change at 12 weeks after surgery compared with pre-operative levels	Body composition Hematologic and biochemical data Quality of life (using EORTC)	EN Otsuka Pharmaceutical Company Ltd
Imamura 2016 [42]	111	Curative distal gastrectomy or total gastrectomy for gastric adenocarcinoma	Percentage of body weight loss (%BWL) between pre-surgery and 6–8 weeks after oral diet commences	Adherence to ED Changes in nutrition-related blood parameters (serum albumin, total protein, total cholesterol, total lymphocyte count) Frequency and severity of adverse events	Not reported
Kong 2018 [41]	127	Distal, total, proximal or pylorus preserving gastrectomy	Incidence of postoperative complications that had a severity of grade II or more (defined by the Clavien-Dindo classifications) within 30 days after the surgery	Body weight changes Length of hospital stay Quality of life Postoperative 20 day mortality Biochemical assessment of nutritional status Compliance with ONS	Abbott Laboratories
Kong 2017 [40]	162	Major gastrointestinal surgery (resection of part/all of the gastrointestinal organ)	Body weight change (%) at 8 weeks after discharge compared to preoperative weight	Changes in body weight compared with pre-operative measurements BMI Patient-generated subjective global assessment score/grade Haematological/biochemical parameters (cholesterol, total protein, albumin, WBC, total lymphocyte count, haemoglobin) Adverse events evaluated at week 2, 4 and 8 after discharge PGSAs	Korean Society of Surgical metabolism and Nutrition
Meng 2021 [39]	377	Gastric cancer	Nutritional outcomes at 3 months compared to baseline (weight, BMI, SMI) Sarcopenia prevalence	Chemotherapy tolerance 90-day readmission rate Quality of life (EORTC)	China Postdoctoral Science Foundation, Shanghai Sailing Program, Municipal Natural Foundation of Shanghai of China, Construction Program of Key but Weak Disciplines of Shanghai health Commision-Clinical Nutrition and Youth Science Foundation of Zhongshan Hospital, Fudan University
Meng 1999 [38]	44	Hepatic resection with curative intent for HCC which developed a cirrhotic liver	Adverse reactions to OS	Height Weight compared with weight at hospital discharge MAC TSF GI upset Neuropsychiatric symptoms Haemoglobin Sodium Albumin Bilirubin Prothrombin time Activated thromboplastin time Survival and reoccurrence	Otsuka pharmaceutical Company (Tokyo, Japan)

Table 1 (*continued*)

Study, Year	No of participants	Type of surgery	Primary endpoint	Secondary endpoint	Source of Funding
Miyazaki 2021 [37]	880	Distal, proximal or total gastrectomy for primary gastric cancer	% body weight loss 1 year after gastrectomy	% body weight loss 3 months after gastrectomy compared with pre-operative measurements Lymphocyte count Hb count CRP Total protein Albumin Total cholesterol AST ALT Bilirubin Creatinine Severity of complications	Partially funded by Supporting Centre for Clinical Research and Education (supported by Otsuka Pharmaceutical and Racol). Authors have received individual funding for lecture fees.
Okabayashi 2011 [36]	76	Elective liver resection to treat hepatocellular carcinoma or adenocarcinoma of liver	Laboratory tests Post operative QoL (using SF-36 scale) Patient compliance	Body weight AMC TSF*	Ministry of Education, Culture, Sports, Science and Technology, The Uehara Memorial Foundation and the Kochi University Discretionary Fund
Smedley 2004 [35]	79	Elective moderate to major lower gastrointestinal surgery	Postoperative change in bodyweight compared with recruitment	Clinical complications Length of hospital stay Nutritional status QofL Cost of care	Numico Research, Wageningen
Tan 2021 [34]	212	Colorectal cancer	Weight loss within three months after discharge compared with hospital discharge BMI SMI Serum levels of albumin Serum Hb levels Sarcopenia prevalence	90-day readmission rate Chemotherapy tolerance Quality of life (using EORTC scale)	China doctoral Science Foundation, Shanghai Sailing Program, Municipal natural Science Foundation of Shanghai of China, Construction Program of Key but Weak Disciplines of Shanghai Health Commission-Clinical Nutrition, Youth Science Foundation of Zhongshan Hospital
Xie 2021 [33]	64	Oesophageal cancer (McKeown oesophagectomy)	% Body Weight Loss compared with presurgical bodyweight	BMI change Compliance Nutrition related adverse events Quality of Life	China Cancer Foundation Beijing Hope Marathon Fund, Special Program for Basic Resource Survey of the Ministry of Science and Technology and Project of Incentive Program for Talent Introduction
Zhu 2019 [32]	114	Gastric or colorectal cancer	Weight compared to baseline BMI Upper arm circumference Hand grip strength TSF	HGB Prealbumin Albumin Total cholesterol Triglycerides Gastrointestinal status score EQ-5D score (quality of life)	Abbott Nutrition

12 of the studies, the participants in the control arms received a standard diet (some also received dietary advice). For the other two studies, the control group consumed an isocaloric and isonitrogenous diet compared with the ONS group [36,38]. The mean daily caloric intake provided by the supplements was 520.9 kcal and the mean protein was 25.5 g. A description of the nutritional interventions used in each of the studies is included in Table 2.

3.3. Primary outcome: weight loss

Eleven studies provided relevant data on change in weight, six presented data in the form of loss of weight (kg) and five presented the data in the form of % BWL. Overall, patients receiving ONS had lost less weight (kg) postoperatively compared with the control group (WMD -1.69 kg, 95% CI -2.98 to −0.41, P = 0.01, I^2 = 98%) (Fig. 2). There was less statistical heterogeneity in the studies presenting data on gastrectomies alone [39,42,43], (WMD -1.32 (95% CI -1.84 to -0.80, P = 0.01, I^2 = 23%). In the analysis using % BWL, there was also a significantly smaller weight loss in the patients taking the supplement, in comparison to the control group: WMD -0.35%, 95% CI -0..65 to -0.05, P = 0.02, I^2 = 22% (Fig. 2). It is of note that despite the statistical significance, there was considerable heterogeneity for this primary outcome.

3.4. Secondary outcomes

There was no difference in total protein concentration between the ONS and control groups (WMD 0.21 g/L, 95% CI -0.22 to 0.65, P = 0.34, I^2 = 14%) (Fig. 3). There was a higher serum albumin concentration in the ONS group compared with the control group (WMD 1.06 g/L, 95% CI 0.04 to 2.07, P = 0.04, I^2 = 84%) (Fig. 3). Serum prealbumin showed no difference between the ONS and control group (WMD 3.47 g/L, 95% CI -2.02 to 8.96, P = 0.21, I^2 = 0%) (Fig. 3). Total lymphocyte count did not differ between the groups (WMD 0.06 × 10^9/L, 95% CI -0.01 to 0.13, P = 0.08, I^2 = 67%) (Fig. 3). Haemoglobin was significantly greater in the ONS group compared with the control group: WMD 2.91 g/L, 95% CI 0.58 to

Table 2
Nutritional protocols of studies.

Study, Year	Country	Feeding protocol after discharge	Days of intervention after discharge	Product in treatment group	Recommended dose per day	Protein from recommended dose of ONS per day	Calories from recommended dose of ONS per day	Control
Beattie 2000 [1]	United Kingdom	OS in addition to standard diet	70	Ensure Plus (Ross Laboratories, UK)	400 ml/day	24 g	600 kcal	Standard diet
Chen [44]	China	OS in addition to standard diet	56	Ensure (Ross Laboratories, UK)	1200–1500 ml/day	51.36 g	1380 kcal	Standard diet
Hatao 2017 [43]	Japan and Taiwan	OS in addition to standard diet	84	Concentrated Liquid Diet Anom (Otsuka, Japan)	400 ml/day	20 g	400 kcal	Standard diet
Imamura 2016 [42]	Japan	OS in addition to standard diet	42–56	Elental (Ajinomoto Pharmaceuticals, Japan)	300 ml/day	N/A	300 kcal/day	Standard diet
Kong 2018 [41]	Korea	OS in addition to standard diet	28	Ensure powder sachets (Ross Laboratories, UK)	500 ml/day	18 g	500 kcal	Standard diet
Kong 2017 [40]	Korea	Os in addition to standard diet	56	Encover (EN Otsuka Pharmaceutical, Hanamaki City, Japan)	400 ml/day	N/A	400 kcal	Standard diet
Meng 1999 [38]	Australia	OS with specified protein and calorie diet totalling 80 g protein and 8946kj per day	84	Aminoleban EN (Otsuka Pharmaceutical, Tokyo)	3 packages of Aminoleban per day	40 g	632 kcal	Isonitrogenous and isocaloric diet
Meng 2021 [39]	China	OS in addition to standard diet	90	Nutren Optimum (Nestle Health Science, Switzerland)	500 ml/day	20.5 g	500 kcal	Standard diet and dietary advice
Miyazaki 2021 [37]	Japan	OS in addition to standard diet	90	Racol NF (Otsuka Pharmaceuticals Factory, Tokyo, Japan)	400 ml/day	17.52 g	400 kcal	Standard diet
Okabayashi 2011 [36]	Japan	OS in addition to standard diet	96	Aminoleban EN (Otsuka Pharmaceutical, Tokyo)	50 g twice a day	Not reported	420 kcal	Isocaloric diet
Smedley 2004 [35]	UK	OS in addition to standard diet (4 arm experiment)	28	Fortisip (Nutricia, Wageningen, The Netherlands)	200 ml ad libitum	0.05 g/ml	0.05 g/ml 1.5 kcal/ml (mean 310 kcal per day)	Standard diet
Tan 2021 [34]	China	OS in addition to standard diet and dietary advice	90	Nutren Optimum (Nestle Health Science, Switzerland)	500 ml	20.5 g	500 kcal	Standard diet and dietary advice
Xie 2021 [33]	China	OS in addition to standard diet	28	Not reported	300 ml	Not reported	450 kcal	Standard diet (1400–1600 kcal)
Zhu 2019 [32]	China	OS in addition to standard diet plus dietary guidance	90	Ensure complete (Ross Laboratories, UK)	112 g	17.7 g	500 kcal	Standard diet and dietary guidance

5.25, P = 0.01, I^2 = 81% (Fig. 3). No difference was observed for total cholesterol (WMD 0.03 mmol/L, 95% CI -0.09 to 0.14, P = 0.67, I^2 = 51%) (Fig. 3).

Five studies [33,34,39,41,43] presented quality of life using the European Organisation for Research and Treatment of Cancer (EORTC) scale. For the purpose of this meta-analysis, specifically the ‘Global Health Status’ data were used for the five studies that used the EORTC scale. Overall, there was no improved quality of life recorded in the ONS group compared with the control group (WMD 0.87, 95% CI -1.75 to 3.48, P = 0.52, I^2 = 41%) (Fig. 4). However, there were other studies which compared quality of life using other scales. For example, Beattie et al. [1], measured Quality of Life using the SF-36 scale, and had reported there was better quality of life in the ONS group compared with the control group.

The meta-analysis of studies which included skeletal muscle mass in kg/m^2 [34,39] did show an increase in the ONS group compared with the control (WMD 1.68 kg/m^2, 95% CI 0.69 to 2.68, P = 0.0009, I^2 = 0%). One study found skeletal muscle mass to be 0.7 kg greater in the control group, however, it was deemed inappropriate to enter into the meta-analysis as it reported data in different units [43].

3.5. Heterogeneity and risk of bias

Due to the nature of this study, it included many different patient populations and length and types of interventions, as well as differences in the individual gastrointestinal surgical procedures. As a result, this meant that clinical variability and statistical heterogeneity in this meta-analysis was relatively high, ranging from 0% to 92%. The risk of bias for the studies is summarised in Fig. 5.

4. Discussion

4.1. What this study found?

This systematic review and meta-analysis used the most contemporary data to conclude that post-discharge ONS, reduces weight loss in the gastrointestinal surgical population (compared with control), when measured as either total weight loss in kg from baseline, or as a percentage of total BWL. There was also an improvement in other parameters (such as serum albumin concentration and haemoglobin).

4.2. What is already known?

Previously, there has been disparity over the effectiveness of ONS. One study found that there was a ‘very low quality of evidence’ supporting the use of ONS to improve weight, energy and protein levels in the post-discharge period [45]. Another reported that there was increasing evidence to support the use of ONS in clinical practice, especially in the acutely ill and older populations [46]. A recent study looking at ONS in postoperative patients with upper gastrointestinal cancer, concluded that home enteral nutrition was more effective than ONS at improving nutritional status in patients undergoing upper gastrointestinal resection [23]. Another review investigating ONS in the discharge period, found little clinical benefit to using ONS post-discharge, but still declared benefit in recommending ONS to high-risk patients [21].

The varying extents of weight loss attenuation across the studies, could be explained by higher patient compliance, a longer postoperative period of feeding in hospital, or the patient population (e.g., there was a greater attenuation of weight loss in patients undergoing surgery for gastric cancer compared with hepatectomy). It also could have been explained by the composition of ONS

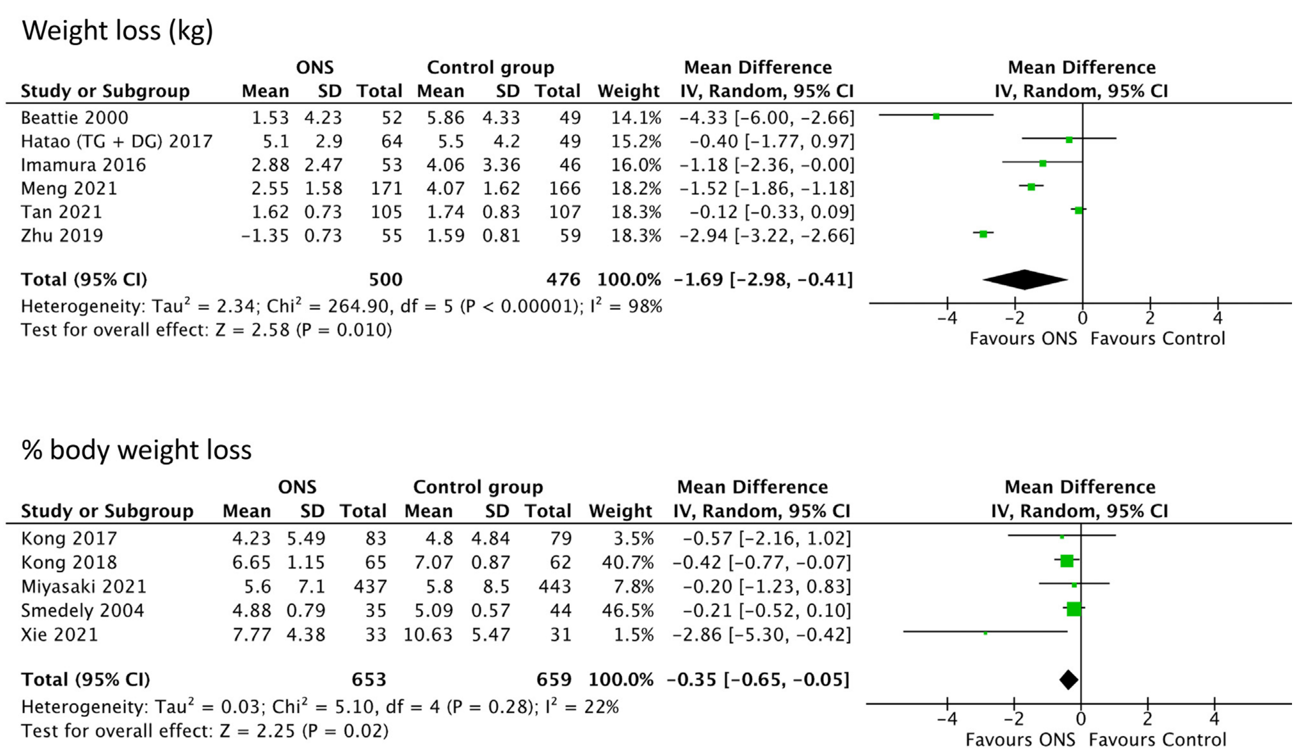

Fig. 2. Forest plots of overall weight loss (kg) (top) and % body weight loss (bottom). DG=distal gastrectomy, TG=total gastrectomy.

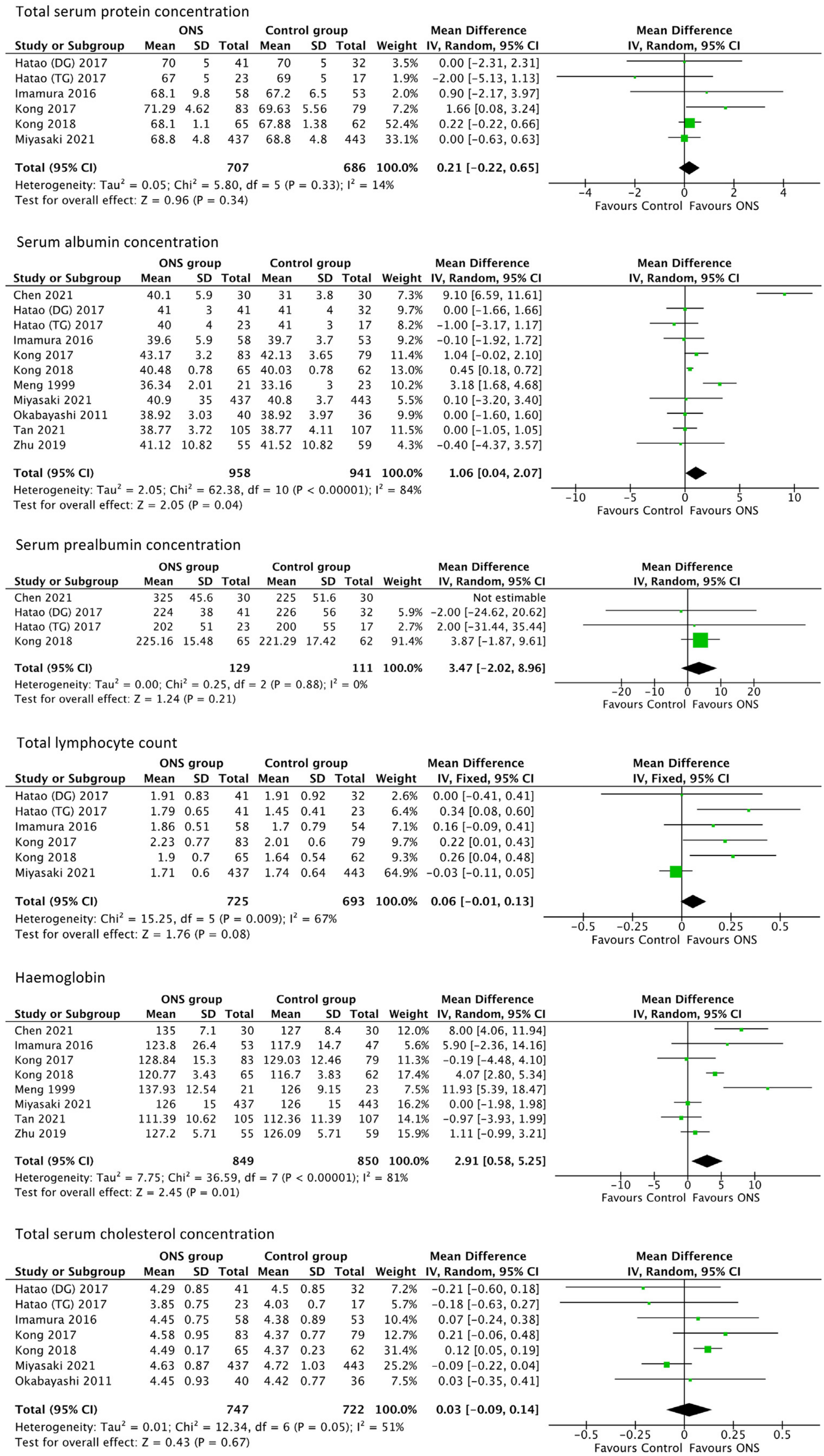

Fig. 3. Forest plots of secondary end points – total protein concentration, serum albumin concentration, serum prealbumin concentration, total lymphocyte count, haemoglobin and total cholesterol concentration. The Hatao study [43] described results separately for distal gastrectomy (DG) and total gastrectomy (TG).

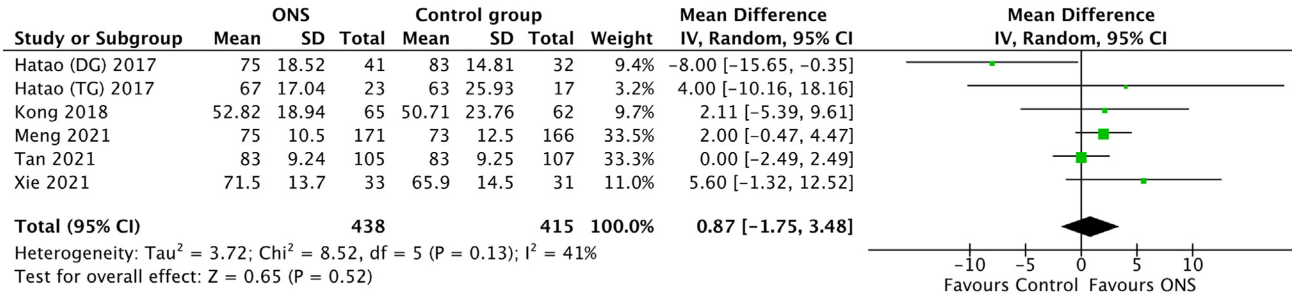

Fig. 4. Forest plot of quality of life analysis. The Hatao study [43] described quality of life separately for distal gastrectomy (DG) and total gastrectomy (TG).

used in the studies. Out of the six studies used to measure the primary outcome of weight loss (in kg), on average 466 kcal and 20.5 g protein were provided by the supplements per day. The study that provided the highest calories and protein in the ONS group (600 kcal and 24 g protein/day) [1], showed a greater reduction in weight loss in the ONS group compared with the other 5 studies. Owing to the greater availability of macronutrients in this study [1] compared with the other studies, one could interpret that the higher caloric and protein supplements, were more effective in preventing weight loss. However, as previously stated in the results, the heterogeneity for weight loss (kg) was high. A subgroup analysis of only studies involving gastrectomies, showed a similar reduction in postoperative weight loss in the ONS group but with lower statistical heterogeneity ($I^2 = 23\%$). Arguably, the high statistical heterogeneity is inevitable when one considers the degree of clinical variability in supplement type and amounts, patient subpopulations, and lifestyle factors across the studies. Another controversy regarding the efficacy of ONS, is a question of compliance. Patients undergoing gastrointestinal surgery often have a reduced appetite following surgery [47], and the additional supplements could increase satiety, leading to a reduced consumption of normal meals. It is difficult to quantify food intake accurately in the post-discharge period and this may be one of the reasons for the relative lack of benefit of ONS on some of the outcome parameters.

Supplements are indicated as an adjunct to normal meals, therefore, if they become a replacement, the overall intake could have little difference to consuming normal meals alone. This has been highlighted in two of the studies [36,38], where patients in the control group were given isocaloric and isonitrogenous intakes compared with the ONS group. There was no difference in weight loss between these two groups. However, to counter this point, the control groups in the aforementioned studies [36,38] were tightly regulated in terms of intake and compliance, which is not something that can be easily mirrored in the general population, owing to resource constraints. This is seen in the rest of the studies, where patients in the control groups were free to make their own meal choices (more generalisable to the real-world population), and here there was a reduced weight loss in the ONS group. It is also of note, that different patient groups within the gastrointestinal surgical population have varying degrees of vulnerabilities for weight loss [42,43].

Unfortunately, there is not a clear, distinct list of nutritional parameters used to objectively define nutritional status. There are various screening tools, which incorporate different parameters. A recent study has explored the associations of albumin and pre-albumin as representatives of malnutrition [48]. Albumin can be decreased during periods of decreased synthesis and prealbumin concentrations <0.11 g/L have been associated with increased mortality and length of hospital stay [49]. Overall, albumin was increased in the ONS group, whereas when pre-albumin was analysed, there was no difference. This contrast could be attributed to the fact that prealbumin has a shorter half-life [48], and as the length of intervention was around 90 days, the difference in pre-albumin was less apparent by the time it was measured. A recent study has shown that although serum prealbumin concentration may be a prognostic indicator, it does not predict the response to nutritional therapy [50]. In addition, it must be noted that serum albumin concentrations are also influenced by inflammation [51] and fluid balance [52] and are not necessarily a marker of nutritional status [53]. It has been estimated that even metabolically healthy patients lose 40–80 g of nitrogen after elective abdominal surgery, and the negative nitrogen balance during the peri-operative catabolic period can lead to muscle loss [54]. Increased protein intake in the ONS group, supports the notion that the ONS group were more likely to have less muscle mass (and overall weight) loss. From the meta-analysis of skeletal muscle mass, the included two studies favoured the ONS group. However, there was another study which favoured the control group [43]. This difference could be due to the discrepancy in how the skeletal muscle mass was measured: one study [43] did not take into account both the skeletal muscle area and the height of the patient, which could have led to a less contextualised conclusion. However, overall, the skeletal muscle mass was higher in the ONS group. This itself is an important finding: as recent research has shown that postoperative skeletal muscle loss is predictive of poorer survival rates [34]. Nonetheless, more studies measuring skeletal muscle mass changes (using the same units and methodology) are required to make a more concrete conclusion. Bed rest, even in healthy volunteers has adverse effects on muscle mass and function [55] and the impact of concurrent exercise with ONS needs to be researched and addressed, as in certain studies it has been shown that exercise and supplements together are beneficial for body composition and muscle strength [56–58].

Serum cholesterol concentrations (LDL-C) have been shown to have a U-shaped relationship with mortality, and low levels have been associated with increased mortality [59]. Lymphocyte counts can also be decreased in malnourished patients due to a reduction in maturation of lymphocytes [60]. This is further supported by recent findings that CD4, CD8 T-cell counts and IgA, IgG and IgM antibodies have all been significantly greater in elderly patients who have undergone surgery for oesophageal cancer [44]. However, in the present analysis, no statistically significant difference in cholesterol concentration or total lymphocyte count was found between the groups. Reduction in haemoglobin is associated with a poor response to illness, and a recent study found that haemoglobin showed a positive correlation with body mass index [61]. This evidence supports the use of ONS in the post-discharge period, as patients are vulnerable to weight loss, as could further support the notion that ONS has a role in preserving or increasing nutritional status of the patient.

Fig. 5. Risk of bias analysis.

Quality of life was a difficult outcome to pool data from. This was because there was a variety of scales used across the 14 studies. The EORTC scale was preferentially used for sub-group analyses as it was the most prevalent scale across the included studies. However, as not all studies which measured quality of life were included, this needs further investigation. Additionally, a more consistent quality of life assessment tool should be advocated for in future nutritional studies, in order to increase the reliability of meta-analyses.

Individually, none of these nutritional markers are particularly sensitive or specific for nutritional status: as previously mentioned, it is the cumulative effect of the markers which builds a more representative and coherent picture of nutritional status. As it is widely disputed what is the ‘gold-standard’ for assessing nutritional status (and a wide range of tools used every day), the patterns observed across the large range of parameters assessed in this study are much more convincing of the benefits of ONS compared with using a few non-specific and non-sensitive parameters alone. It has been speculated (and studied to a degree) about surgical nutrition being linked to the marginal gains theory. This theory involves multiple nutritional interventions, each with small benefits to accumulate to make a more significant improvement to nutritional health [62]. In this context, it is hypothesised that using both preoperative and postoperative ONS (potentially as well as incorporating exercise rehabilitation and dietary advice), will have the maximum benefit to the patient. Another factor that needs exploring is the economic benefit of ONS. One study showed that ONS was cost-effective, with end-cost being the highest in the control group [35]. This was augmented in the more recent meta-analysis, whereby ONS was shown to have positive economic impact on patients with gastrointestinal cancer [63].

4.3. Limitations of study

The main limitation of this review is the high clinical heterogeneity across the studies. Each RCT had different assigned outcomes, patient groups, type of supplement and duration of intervention. In addition, the baseline data measured in the different studies were taken at different time-points: some studies took initial measurements preoperatively, whereas others chose to take baseline data at recruitment to the study or at discharge. Consequently, these discrepancies lend reasoning to the difference in overall weight loss or change in parameters across the studies and additionally the statistical heterogeneity across some of the results. Furthermore, although the conclusions can be used generically to advocate the use of ONS in the post-discharge period, it is not yet clear, which patients would benefit the most, or which type and length of intervention would be most effective. There is some evidence from this review, that the higher energy and protein containing supplements are of more benefit, however this can be disputed by the theory of increased satiety leading to poor compliance. In addition, many of the studies presented outcome data graphically rather than numerically. Despite requesting access for these data, the required information was not obtained. Therefore, interpolation via WebPlotDigitiser was used in some cases to extract the necessary information, and Cochrane Handbook approved software was used to estimate the standard deviation using appropriate values. Many of the included trials received funding from the commercial company that produced the nutritional supplements: though mostly it was declared that the author was independent from the company, this has been noted during the bias assessment. It must also be touched upon, that although the RCTs included a range of European, Asian and Australian countries, there were a lack of studies carried out in more economically deprived countries. This reduces the generalisability of the overall results from the review to populations from low- and middle-income countries, as different cultures have different diet compositions and levels of malnutrition. For example, it has been noted that there is a particularly high prevalence of post-operative nutritional deficits in Asian patients undergoing surgery [64]: ONS interventions could consequently be more/less effective in these groups. Finally, there were two studies in the Chinese language which met the criteria for inclusion, however it was not possible to obtain translation (due to time and resource constraints).

One of the difficulties in studies on nutritional interventions is identifying patients who are most likely to benefit. While nutritional risk and assessment tools are beneficial in identifying malnutrition, they do not help predict outcome [65,66]. Most of the studies in this meta-analysis did not comment on clinical outcomes and it is not certain if complications that occurred after discharge were missed. Additionally, although quality of life and fatigue are interesting end points, it is surprising that there was no difference between the groups.

5. Future directions and conclusions

Overall, the results from this meta-analysis support the use of post-discharge nutritional supplements in patients undergoing gastrointestinal surgery, due to the improvement in some biochemical parameters and attenuation of weight loss. However, this area requires larger, multi-centre trials to support this further, including multi-armed trials which incorporate preoperative and postoperative supplements and also exercise and diet counselling. The cost-effectiveness of the latter should also be further explored. There should also be further research into patient's views on supplements (regarding taste, preference, side effects and satiety) and the effect on patient compliance. A recent trial has recommended diversification of ONS products and improved patient education regarding management of adverse reactions [67]. Attention should be paid to this in future guidelines and manufacturing processes to augment compliance and cost-effectiveness. Even if ONS is not given universally to patients undergoing gastrointestinal surgery, the most vulnerable and at-risk patient groups need to be identified. It is likely that patients undergoing surgery for colorectal, gastric, pancreatic and oesophageal cancers could experience the most benefit from ONS interventions. Finally, a large interference in carrying out this meta-analysis, was the lack of consistency in units and the way outcomes were measured across the trials. International societies focused on clinical nutrition could help define a set of ‘gold-standard’ or core outcomes to be used in future trials, including the presentation of data in the form of SI units, as it would increase the reliability of future nutritional meta-analyses.

Author contributions

Study design: AR, AA, AK, SJL, DNL.
Data extraction: AR, AA, AK.
Data analysis: AR, AA.
Data interpretation: AR, AA, AK, SJL, DNL.
Writing of the manuscript: AR, AA, DNL.
Critical review: AR, AA, SJL, DNL.
Approval of submitted manuscript: AR, AA, AK, SJL, DNL.
Overall supervision: DNL.

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Data sharing

Data will be available upon reasonable request from DNL (dileep.lobo@nottingham.ac.uk).

Ethical statement

As this was a systematic review and meta-analysis, ethics committee approval was not necessary. The protocol was registered with the PROSPERO database. The registration number is CRD42020196375 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=196375).

Conference presentation

A preliminary version of this paper was presented to the Annual Meeting of the Surgical Research Society, Nottingham, UK in March 2022. This has been published in abstract form: *Br J Surg* 2022; 109(Supplement_4): znac242.015.

Conflict of interest

DNL has received an unrestricted educational grant from B. Braun for unrelated work. He has also received speaker's honoraria for unrelated work from Abbott, Nestlé and Corza.

None of the other authors has a direct conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.04.028.

References

[1] Beattie AH, Prach AT, Baxter JP, Pennington CR. A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. Gut 2000;46:813–8.
[2] Weiss AJ, Fingar KR, Barrett ML, Elixhauser A, Steiner CA, Guenter P, et al. Characteristics of hospital stays involving malnutrition. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013. 2006.
[3] Amaral TF, Matos LC, Tavares MM, Subtil A, Martins R, Nazare M, et al. The economic impact of disease-related malnutrition at hospital admission. Clin Nutr 2007;26:778–84.
[4] Correia MITD. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. Clin Nutr 2003;22:235–9.
[5] Curtis LJ, Bernier P, Jeejeebhoy K, Allard J, Duerksen D, Gramlich L, et al. Costs of hospital malnutrition. Clin Nutr 2017;36:1391–6.
[6] Baker M, Halliday V, Williams RN, Bowrey DJ. A systematic review of the nutritional consequences of esophagectomy. Clin Nutr 2016;35:987–94.
[7] Mosquera C, Koutlas NJ, Edwards KC, Strickland A, Vohra NA, Zervos EE, et al. Impact of malnutrition on gastrointestinal surgical patients. J Surg Res 2016;205:95–101.
[8] Van Cutsem E, Arends J. The causes and consequences of cancer-associated malnutrition. Eur J Oncol Nurs 2005;9(Suppl 2):S51–63.
[9] Djarv T, Blazeby JM, Lagergren P. Predictors of postoperative quality of life after esophagectomy for cancer. J Clin Oncol 2009;27:1963–8.
[10] Mans E, Serra-Prat M, Palomera E, Sunol X, Clave P. Sleeve gastrectomy effects on hunger, satiation, and gastrointestinal hormone and motility responses after a liquid meal test. Am J Clin Nutr 2015;102:540–7.
[11] Shpata V, Prendushi X, Kreka M, Kola I, Kurti F, Ohri I. Malnutrition at the time of surgery affects negatively the clinical outcome of critically ill patients with gastrointestinal cancer. Med Arch 2014;68:263–7.
[12] Huber-Lang M, Lambris JD, Ward PA. Innate responses to trauma. Nat Immunol 2018;19:327–41.
[13] Varadhan KK, Constantin-Teodosiu D, Constantin D, Greenhaff PL, Lobo DN. Inflammation-mediated muscle metabolic dysregulation local and remote to the site of major abdominal surgery. Clin Nutr 2018;37:2178–85.
[14] Manou-Stathopoulou V, Korbonits M, Ackland GL. Redefining the perioperative stress response: a narrative review. Br J Anaesth 2019;123:570–83.
[15] Wobith M, Weimann A. Oral nutritional supplements and enteral nutrition in patients with gastrointestinal surgery. Nutrients 2021;13:2655.
[16] Simsek T, Simsek HU, Canturk NZ. Response to trauma and metabolic changes: posttraumatic metabolism. Ulus Cerrahi Derg 2014;30:153–9.
[17] Lobo DN, Gianotti L, Adiamah A, Barazzoni R, Deutz NEP, Dhatariya K, et al. Perioperative nutrition: recommendations from the ESPEN expert group. Clin Nutr 2020;39:3211–27.
[18] Weimann A, Braga M, Carli F, Higashiguchi T, Hubner M, Klek S, et al. ESPEN practical guideline: clinical nutrition in surgery. Clin Nutr 2021;40:4745–61.
[19] Hubert M, Gabriel D, El Khouda S, Coster M, Routiaux C, Hans G, et al. Energy and protein intake after return home in colorectal surgery patients with an enhanced recovery program: a prospective observational study. Nutr Clin Pract 2021;36:639–47.
[20] National Institute for Health and Care Excellence. Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition. London: NICE; 2006. updated 2017.
[21] Lidder PG, Lewis S, Duxbury M, Thomas S. Systematic review of postdischarge oral nutritional supplementation in patients undergoing GI surgery. Nutr Clin Pract 2009;24:388–94.
[22] Crickmer M, Dunne CP, O'Regan A, Coffey JC, Dunne SS. Benefits of post-operative oral protein supplementation in gastrointestinal surgery patients: a systematic review of clinical trials. World J Gastrointest Surg 2016;8:521–32.
[23] Xueting H, li L, Meng Y, Yuqing C, Yutong H, Lihong Q, et al. Home enteral nutrition and oral nutritional supplements in postoperative patients with upper gastrointestinal malignancy: a systematic review and meta-analysis. Clin Nutr 2021;40:3082–93.
[24] Elia M, Russell CA. Combating malnutrition: recommendations for action. Nutrition advisory group on malnutrition led by BAPEN 2009. Redditch: The British Association for Parenteral and Enteral Nutrition (BAPEN); 2009.
[25] Deftereos I, Yeung JM, Arslan J, Carter VM, Isenring E, Kiss N, et al. Adherence to ESPEN guidelines and associations with postoperative outcomes in upper gastrointestinal cancer resection: results from the multi-centre NOURISH point prevalence study. Clin Nutr ESPEN 2022;47:391–8.
[26] Review Manager [Computer program]. The Cochrane Collaboration 2020. Version 5.4.1.
[27] Deeks JJ, Higgins JPT, Altman DG. Chapter 10: analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane Handbook for systematic reviews of interventions version 6.3. Cochrane; 2022.
[28] Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane Handbook for systematic reviews of interventions version 6.3 (updated February 2022). Cochrane; 2022.
[29] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. J Clin Epidemiol 2021;134:178–89.
[30] Jensen MB, Hessov I. Randomization to nutritional intervention at home did not improve postoperative function, fatigue or well-being. Br J Surg 1997;84:113–8.
[31] Keele AM, Bray MJ, Emery PW, Duncan HD, Silk DBA. Two phase randomised controlled clinical trial of postoperative oral dietary supplements in surgical patients. Gut 1997;40:393–9.
[32] Zhu MW, Yang X, Xiu DR, Yang Y, Li GX, Hu WG, et al. Effect of oral nutritional supplementation on the post-discharge nutritional status and quality of life of gastrointestinal cancer patients after surgery: a multi-center study. Asia Pac J Clin Nutr 2019;28(3):450–6.
[33] Xie H, Chen X, Xu L, Zhang R, Kang X, Wei X, et al. A randomized controlled trial of oral nutritional supplementation versus standard diet following McKeown minimally invasive esophagectomy in patients with esophageal malignancy: a pilot study. Ann Transl Med 2021;9:1674.
[34] Tan S, Meng Q, Jiang Y, Zhuang Q, Xi Q, Xu J, et al. Impact of oral nutritional supplements in post-discharge patients at nutritional risk following colorectal cancer surgery: a randomised clinical trial. Clin Nutr 2021;40:47–53.
[35] Smedley F, Bowling T, James M, Stokes E, Goodger C, O'Connor O, et al. Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care. Br J Surg 2004;91:983–90.
[36] Okabayashi T, Iyoki M, Sugimoto T, Kobayashi M, Hanazaki K. Oral supplementation with carbohydrate- and branched-chain amino acid-enriched nutrients improves postoperative quality of life in patients undergoing hepatic resection. Amino Acids 2011;40:1213–20.
[37] Miyazaki Y, Omori T, Fujitani K, Fujita J, Kawabata R, Imamura H, et al. Oral nutritional supplements versus a regular diet alone for body weight loss after gastrectomy: a phase 3, multicenter, open-label randomized controlled trial. Gastric Cancer 2021;24:1150–9.
[38] Meng WC, Leung KL, Ho RL, Leung TW, Lau WY. Prospective randomized control study on the effect of branched-chain amino acids in patients with liver resection for hepatocellular carcinoma. Aust N Z J Surg 1999;69:811–5.
[39] Meng Q, Tan S, Jiang Y, Han J, Xi Q, Zhuang Q, et al. Post-discharge oral nutritional supplements with dietary advice in patients at nutritional risk after surgery for gastric cancer: a randomized clinical trial. Clin Nutr 2021;40:40–6.

[40] Kong SH, Park JS, Lee IK, Ryu SW, Park YK, Yang HK, et al. Postoperative oral nutritional supplementation after major gastrointestinal surgery: a randomized controlled clinical trial. Asia Pac J Clin Nutr 2017;26:811–9.
[41] Kong SH, Lee HJ, Na JR, Kim WG, Han DS, Park SH, et al. Effect of perioperative oral nutritional supplementation in malnourished patients who undergo gastrectomy: a prospective randomized trial. Surgery 2018;164:1263–70.
[42] Imamura H, Nishikawa K, Kishi K, Inoue K, Matsuyama J, Akamaru Y, et al. Effects of an oral elemental nutritional supplement on post-gastrectomy body weight loss in gastric cancer patients: a randomized controlled clinical trial. Ann Surg Oncol 2016;23:2928–35.
[43] Hatao F, Chen KY, Wu JM, Wang MY, Aikou S, Onoyama H, et al. Randomized controlled clinical trial assessing the effects of oral nutritional supplements in postoperative gastric cancer patients. Langenbeck's Arch Surg 2017;402:203–11.
[44] Chen X, Zhao G, Zhu L. Home enteral nutrition for postoperative elderly patients with esophageal cancer. Ann Palliat Med 2021;10:278–84.
[45] Reece L, Hogan S, Allman-Farinelli M, Carey S. Oral nutrition interventions in patients undergoing gastrointestinal surgery for cancer: a systematic literature review. Support Care Cancer 2020;28:5673–91.
[46] Stratton RJ, Elia M. A review of reviews: a new look at the evidence for oral nutritional supplements in clinical practice. Clin Nutr Suppl 2007;2:5–23.
[47] Wagner M, Probst P, Haselbeck-Kobler M, Brandenburg JM, Kalkum E, Storzinger D, et al. The problem of appetite loss after major abdominal surgery: a systematic review. Ann Surg 2022;276:256–69.
[48] Keller U. Nutritional laboratory markers in malnutrition. J Clin Med 2019;8:775.
[49] Delliere S, Cynober L. Is transthyretin a good marker of nutritional status? Clin Nutr 2017;36:364–70.
[50] Bretscher C, Buergin M, Gurzeler G, Kagi-Braun N, Gressies C, Tribolet P, et al. Association between prealbumin, all-cause mortality and response to nutritional treatment in patients at nutritional risk: secondary analysis of a randomized controlled trial. JPEN - J Parenter Enter Nutr 2023;47:408–19.
[51] Bretscher C, Boesiger F, Kaegi-Braun N, Hersberger L, Lobo DN, Evans DC, et al. Admission serum albumin concentrations and response to nutritional therapy in hospitalised patients at malnutrition risk: secondary analysis of a randomised clinical trial. EClinicalMedicine 2022;45:101301.
[52] Lobo DN, Stanga Z, Simpson JA, Anderson JA, Rowlands BJ, Allison SP. Dilution and redistribution effects of rapid 2-litre infusions of 0.9% (w/v) saline and 5% (w/v) dextrose on haematological parameters and serum biochemistry in normal subjects: a double-blind crossover study. Clin Sci 2001;101:173–9.
[53] Schuetz P, Seres D, Lobo DN, Gomes F, Kaegi-Braun N, Stanga Z. Management of disease-related malnutrition for patients being treated in hospital. Lancet 2021;398:1927–38.
[54] Scott MJ, Baldini G, Fearon KC, Feldheiser A, Feldman LS, Gan TJ, et al. Enhanced Recovery after Surgery (ERAS) for gastrointestinal surgery, part 1: pathophysiological considerations. Acta Anaesthesiol Scand 2015;59:1212–31.
[55] Shur NF, Simpson EJ, Crossland H, Chivaka PK, Constantin D, Cordon SM, et al. Human adaptation to immobilization: novel insights of impacts on glucose disposal and fuel utilization. J Cachexia Sarcopenia Muscle 2022;13:2999–3013.
[56] Oppert JM, Bellicha A, Roda C, Bouillot JL, Torcivia A, Clement K, et al. Resistance training and protein supplementation increase strength after bariatric surgery: a randomized controlled trial. Obesity 2018;26:1709–20.
[57] Hirsch KR, Blue MNM, Trexler ET, Ahuja S, Smith-Ryan AE. Provision of ready-to-drink protein following bariatric surgery: an evaluation of tolerability, body composition, and metabolic rate. Clin Nutr 2021;40:2319–27.
[58] Lopez-Rodriguez-Arias F, Sanchez-Guillen L, Aranaz-Ostariz V, Triguero-Canovas D, Lario-Perez S, Barber-Valles X, et al. Effect of home-based prehabilitation in an enhanced recovery after surgery program for patients undergoing colorectal cancer surgery during the COVID-19 pandemic. Support Care Cancer 2021;29:7785–91.
[59] Johannesen CDL, Langsted A, Mortensen MB, Nordestgaard BG. Association between low density lipoprotein and all cause and cause specific mortality in Denmark: prospective cohort study. BMJ 2020;371:m4266.
[60] Lobo DN, Allison SP. Nutritional support and functional recovery. Curr Opin Clin Nutr Metab Care 2000;3:129–34.
[61] Sayed SF, Nagarajan S. Haemoglobin status to determine nutritional anaemia and its association with breakfast skipping and BMI among nursing undergraduates of Farasan Island. KSA. J Nutr Sci. 2022;11:e36.
[62] Adiamah A, Lobo DN. Post-discharge oral nutritional supplementation after surgery for gastrointestinal cancer: real or marginal gains? Clin Nutr 2021;40:1–3.
[63] Zhu M, Chen W, Jiang H, Zhu S, Xu J, Bao W, et al. Economic value of nutritional support methods in gastrointestinal cancer: a quantitative meta-analysis. Asia Pac J Clin Nutr 2020;29:83–93.
[64] Seo JM, Joshi R, Chaudhary A, Hsu HS, Trung LV, Inciong JF, et al. A multinational observational study of clinical nutrition practice in patients undergoing major gastrointestinal surgery: the Nutrition Insights Day. Clin Nutr ESPEN 2021;41:254–60.
[65] Kaegi-Braun N, Boesiger F, Tribolet P, Gomes F, Kutz A, Hoess C, et al. Validation of modified GLIM criteria to predict adverse clinical outcome and response to nutritional treatment: a secondary analysis of a randomized clinical trial. Clin Nutr 2022;41:795–804.
[66] Stalder L, Kaegi-Braun N, Gressies C, Gregoriano C, Tribolet P, Lobo DN, et al. Prospective validation of five malnutrition screening and assessment instruments among medical inpatients: secondary analysis of a randomized clinical trial. Clin Nutr 2022;41:1307–15.
[67] Wan GY, Yuan H, Xue H, Li HQ, Hu HY, Zhang XY. Assessment of compliance with oral nutritional supplementation and exploration of barriers and facilitators for patients after gastrectomy: a mixed-methods study. J Adv Nurs 2021;77:2845–59.