Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Early Oral Protein-Containing Diets Following Elective Lower Gastrointestinal Tract Surgery in Adults: A Meta-Analysis of Randomized Clinical Trials.

Hong PU
Sichuan University West China Hospital
Philippa T. Heighes
University of Sydney
Fiona Simpson
University of Sydney
Yaoli WANG
Third Military Medical University Daping Hospital and Research Institute of Surgery
Zeping LIANG
Third Military Medical University Daping Hospital and Research Institute of Surgery
Paul Wischmeyer
Duke University School of Medicine
Thomas J. Hugh
University of Sydney
Gordon S. Doig (gdoig@med.usyd.edu.au)
The University of Sydney

Research

Keywords: postoperative nutrition, protein, elective surgery, meta-analysis, mortality

Posted Date: May 19th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-29449/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Version of Record: A version of this preprint was published on March 23rd, 2021. See the published version at https://doi.org/10.1186/s13741-021-00179-3.

Abstract

Background: Although current guidelines make consensus recommendations for the early resumption of oral intake after surgery, a recent comprehensive meta-analysis failed to identify any patient-centred benefits. We hypothesized this finding was attributable to pooling studies providing effective protein-containing diets with ineffective non-protein liquid diets. Therefore, the aim of this paper was to investigate the safety and efficacy of early oral protein-containing diets versus later (traditional) feeding after elective lower gastrointestinal tract surgery in adults.

Methods: PubMed, Embase and the China National Knowledge Infrastructure databases were searched from inception until 1 August 2019. Reference lists of retrieved studies were hand searched to identify randomized clinical trials reporting mortality. No language restrictions were applied. Study selection, risk of bias appraisal and data abstraction were undertaken independently by two authors. Disagreements were settled by obtaining an opinion of a third author. Majority decisions prevailed. After assessment of underlying assumptions, a fixed-effects method was used for analysis. The primary outcome was mortality. Secondary outcomes included surgical site infections, postoperative nausea and vomiting, serious postoperative complications and other key measures of safety and efficacy .

Results: Eight randomized clinical trials recruiting 657 patients were included. Compared with later (traditional) feeding, commencing an early oral protein-containing diet resulted in a statistically significant reduction in mortality (Odds Ratio [OR] 0.31, P =0.02, I 2 =0%). An early oral protein-containing diet also significantly reduced surgical site infections (OR 0.39, P =0.002, I 2 =32%), postoperative nausea and vomiting (OR 0.62, P =0.04, I 2 =37%), serious postoperative complications (OR 0.60, P =0.01, I 2 =25%) and significantly improved other major outcomes. No harms attributable to an early oral protein-containing diet were identified.

Conclusions: The results of this systematic review can be used to upgrade current guideline statements to a Grade A recommendation supporting an oral protein-containing diet commenced before the end of postoperative day 1 after elective lower gastrointestinal surgery in adults.

Background

Early oral intake after elective surgery is considered to be “safe and vital for optimizing postoperative outcomes.”[1] Meta-analyses have shown that, compared to later (traditional) feeding, early oral intake after elective colorectal surgery *may* significantly reduce postoperative infections,[2] serious postoperative complications,[3] anastomotic leaks,[4] and mortality.[5] However, the most comprehensive systematic review and meta-analysis conducted by leading experts on the topic, updated in 2019, failed to confirm any of these previously reported important clinical benefits.[6] All of these previous meta-analyses based their conclusions on a pooled assessment of *protein-containing* diets with *non-protein* liquid diets.

Early initiation of a protein-containing diet has been shown to significantly reduce mortality after urgent or emergency surgery for major trauma [7] and major burn injury.[8] Furthermore, pneumonia, sepsis, gastrointestinal hemorrhage and duration of hospital stay are also significantly reduced in these surgical populations.[7,8] We were unable to find any meta-analyses that explicitly focused on the benefits of an early oral protein-containing diet after elective surgery.

The purpose of this systematic review was to identify, appraise and synthesize evidence from randomized clinical trials (RCTs) evaluating the impact of an early oral protein-containing diet, compared to later (traditional feeding), on outcomes after elective lower gastrointestinal tract surgery in adults. The primary outcome for meta-analysis was mortality.

Materials And Methods

This study was conducted and reported in compliance with established methodological guidelines.[9] Detailed study methods were published on-line in advance of search close-out.[10]

Study selection, risk of bias appraisal and data abstraction were undertaken by two authors. Disagreements were settled by obtaining an opinion of a third independent author. Majority decisions prevailed.

Literature search

Medline (www.PubMed.org), Embase (www.EMBASE.com) and the China National Knowledge Infrastructure (www.CNKI.com.cn) were searched from inception until 1 August 2019. Appropriate database specific statements and terms[7,8] are reported in the Online-only Supplement. Reference lists of retrieved papers were hand searched.

Study selection

All RCTs comparing early oral or enteral nutrition to later (traditional) feeding published in any language were retrieved in full and screened for inclusion. The intervention of interest was defined as oral or enteral intake initiated within 24 hours of surgery using a drink, food or solution that contained calories *and* protein. The comparison group was accepted to include any form of nutrition commenced later than 24 h after surgery. When needed, end of Postoperative Day [POD] 1 was used to define the outer limit for this 24 h period.

RCTs reporting mortality conducted in adult patients who had received surgery to the lower gastrointestinal tract (distal to the ligament of Treitz) were eligible for inclusion and were reviewed in detail.

Risk of bias

Included trials were appraised on the reporting of three key methodological criteria: **1)** maintenance of allocation concealment; **2)** use of blinding and; **3)** completeness of follow-up. Major flaws leading to a recognized high risk of bias were defined *a priori* as clear failure to maintain allocation concealment [11] and excessive (>10%) loss to follow-up.[12]

Outcomes

The primary outcome was mortality, assessed at the longest reported follow-up interval. Secondary outcomes included physical function, quality of life, duration of hospital stay, requirement for intensive care unit (ICU) admission, surgical site infections, anastomotic leak/dehiscence, postoperative nausea and vomiting, pneumonia and need for re-operation. Number of patients with intra-abdominal abscess/peritonitis, severe postoperative complications and postoperative infections were also assessed.

Statistical analysis

The Mantel-Haenszel method was used to calculate the odds ratio (OR) metric unless data was sparse, in which case the Peto method was used.[11, 13] The underlying assumption behind the fixed effects model was assessed with a formal chi-square test of heterogeneity [14] and quantified using the I^2 metric.[15] Important heterogeneity was defined as a P-value for the test of heterogeneity ($P_{heterogeneity}$) less than 0.10 or I^2 greater than 50%.[16] Publication bias was assessed using a Funnel plot of the primary outcome.

Analysis was conducted using RevMan Version 5.3.5 for Windows (The Cochrane CollaborationÒ, Oxford, England, 2014). A two-tailed P-value less than 0.05 was accepted to indicate statistical significance.

Sensitivity analysis

Focused on the primary outcome, the sensitivity analysis considered trials with *less certainty* regarding protein content of the intervention group's early nutrition.

Heterogeneity and stratified analysis

If important heterogeneity was detected, the following *a priori* identified potential sources of heterogeneity were investigated via stratified analysis: **1)** methodological quality; **2)** intervention timing and dose; **3)** co-interventions and comparison intervention received; and **4)** measurement and timing of outcomes.[17]

Results

Literature search and Study selection

The primary literature search identified 2,947 abstracts of potentially eligible studies. Review of retrieved abstracts and hand searching of reference lists of published guidelines and systematic reviews resulted in 196 articles identified for retrieval. Of these 196 articles, 53 RCTs appeared to address key aspects of the primary study question. Eight of these 53 RCTs were deemed eligible for inclusion. **Figure 1** reports the study selection flow. The Online-only Supplement provides additional details regarding RCTs deemed not eligible (**eTable 1**).

The eight included RCTs enrolled 657 participants.[18,19,20,21,22,23,24,25] Primary information regarding each of these eight RCTs was abstracted directly from the publications cited above. Additional information on three RCTs [22,23,25] were available from the systematic review by Herbert *et al*.[6] Herbert *et al.* obtained these additional details by direct correspondence with the authors of these three RCTs.

Two included RCTs established early oral intake by using a protein drink,[18, 24] two RCTs provided enteral nutrition via a feeding tube,[19, 22] and four RCTs commenced a solid diet containing protein on POD 1.[20, 21, 23, 25] Details of the study populations and study interventions are reported in **Table 1.**

Study	Patient population	Protocol for Early Nutrition Intervention	Control
Beier-Holgersen 1996	60 patients with gastrointestinal disease undergoing abdominal surgery (87% underwent colorectal surgery).	Start within 4 h of surgery (POD 0): 60 mls of protein drink (Nutricia Nutridrink, Orange) every hour, for total of 600 ml. POD 1: 1000 ml of protein drink; POD 2: 1400 ml protein drink; POD 3 & 4: 1800 ml protein drink.	Placebo (water with orange flavor) following same protocol as early protein drink group.
Carr 1996	28 patients undergoing intestinal resection distal to the ligament of Treitz.	Start within 2 to 3 h of surgery (POD 0): 25 ml/h EN (Fresubin, Fresenius) via N-J tube. Rate increased by 25 ml every 4 h until target of 35 ml/kg/day achieved.	NPO until passage of flatus.
Lau 2014	111 elective colorectal surgery patients.	Start POD 1: Solid diet that left minimal residue in the lower intestinal tract after digestion and absorption.	Start POD 1: Clear liquids, specifically omitting all solids (Ex. milk, and fruit juice with pulp). POD 2: Advanced to solid diet.
Minig 2009	51 gynecologic oncology patients. (Over 70% also had rectosigmoid resection in addition to hysterectomy.)	Start POD 0: Clear fluids and other liquids (tea, apple juice etc). If fluids tolerated, progress to regular diet by end of POD 1.	NPO until resolution of ileus.
Mulrooney 2004	73 patients undergoing colonic resection	Start within 24 h of surgery: 25 ml/h EN (Nutrison Standard, Nutricia) via N-J tube; POD 2: 50 ml/h EN; POD 3: 75 ml/h: POD 4: EN increased to calculated nutritional targets.	NPO until passage of flatus.
Ortiz 1996	190 patients undergoing elective colon and rectal surgery.	Early removal of NG tube with clear liquids on POD 0 followed by regular diet on POD 1.	NPO until resolution of ileus.
Shen 2013	82 patients with colorectal cancer undergoing surgery.	Start POD 1: 200 mls 0.9% Saline and 200 ml EN; POD 2: 500 to 1000 mls EN; POD 3: 1500 to 2000mls of EN; POD 4: 2000 mls EN continued until POD 7.	Start standard PN POD 2: standard PN continued until POD 7.
Stewart 1998	88 patients undergoing elective colorectal resection with anastomosis, without stoma formation.	Start within 4 h of surgery (POD 0): free fluids; POD 1: Solid diet.	NPO until passage of flatus or bowel movement.

Study	Patient population	Protocol for Early Nutrition Intervention	Control

POD: postoperative day; EN: enteral nutrition solution containing protein, NPO: nil per os, PN: parenteral nutrition solution containing glucose, amino acids and protein, N-J: naso-jejunal tube.

Table 1
Characteristics of included studies

Risk of Bias

Three RCTs explicitly reported the process used to maintain allocation concealment,[19, 20,21] whilst the remaining five were unclear. One study achieved blinding using a placebo intervention.[18] Three studies documented failure to follow-up all randomized patients, with one reporting loss of 6.3% (7/111)[20] of randomized patients, a second reporting 9.1% (8/88) loss [25] and the third documenting loss of 21.5% (11/51) of randomized patients.[21] Based on *a priori* defined criteria,[11, 12] only one study was found to have a major methodological flaw resulting in a high risk of bias.[21] The funnel plot of the primary outcome did not reveal publication bias (**eFigure 1**).

Mortality

Eight RCTs enrolling 657 patients were included in the analysis of mortality. Two studies reported mortality at study day 30,[18, 20] one reported mortality at study day 60,[22] with the remaining five studies reporting mortality at time of hospital discharge. Mortality data for the trial by Mulrooney *et al* [22] was abstracted from the systematic review by Herbert *et al.*[6] Herbert *et al.* reported corresponding with Mulrooney *et al* to obtain this mortality information.

Compared with later (traditional) feeding, commencing an early oral protein-containing diet resulted in a statistically significant reduction in mortality (OR 0.31, 95% Confidence Interval [CI] 0.12 to 0.80, P=0.02, **Figure 2**), with no heterogeneity ($P_{heterogeneity}$=0.95, I^2=0%).

Physical function

Three studies reported measures of physical function. Carr *et al.* reported change in handgrip strength,[19] Stewart *et al.* documented time to mobilization after surgery[25] and Minig *et al.* assessed physical function at study day 30 using the European Organization for Research and Treatment of Cancer (EORTC) C-30.[21]

Carr *et al.* reported a mean 9.6 (Standard Deviation [SD] 2.1) kg loss in handgrip strength in control patients, and a 6.7 (3.2) kg loss in handgrip strength in patients who received an early diet containing protein.[19] Assessed using a standard t-test for differences between groups, patients who received an early diet containing protein experienced significantly less handgrip strength loss (2.9 kg less, 95% CI 0.9 to 4.9kg, P=0.01).

Minig *et al.* failed to find a significant difference between groups with regards to physical function assessed at study day 30 using EORTC C-30 (76.1±14.3 early vs. 62.1±25.3 traditional, P=0.146).[21]

Stewart *et al.* also failed to find a significant difference between groups with regards to time to mobilization after surgery.[25] Stewart *et al.* did not report the actual times to mobilization for each group.

Because of the differences in outcome metrics reported, these measures of physical function could not be pooled.

Quality of life

One RCT reported formal measures of quality of life.[21] Minig *et al.* failed to find a significant difference in EORTC OV-28 assessed at study day 30.

Duration of hospital stay

All eight included RCTs reported duration of hospital stay. One trial reported differences in median hospital stay,[18] with the remaining seven reporting mean (SD). Mean (SD) hospital stay data for the trials by Minig *et al.*, Mulrooney *et al.,* and Stewart *et al.* was abstracted from the systematic review by Herbert *et al.*[6] Herbert *et al.* reported corresponding with these authors to obtain this additional mean (SD) information regarding hospital stay.

Using a non-parametric test, the individual RCT conducted by Beier-Holgersen *et al.* reported a *trend* towards a reduction in median hospital stay for patients who received an early diet containing protein: median 8 vs. 11.5 days (P=0.08).[18]

Meta-analysis of the mean (SD) length of stay data reported by seven RCTs recruiting 598 patients demonstrated a significantly shorter hospital stay for patients randomized to receive an early oral protein-containing diet (-2.12 days, 95% CI -2.74 to -1.49 days, P<0.00001, e**Figure 2**), however, important heterogeneity was detected ($P_{heterogeneity}$=0.00006, I^2=75%). Sources of this heterogeneity are investigated further with stratified analysis (see later in Results).

Intensive Care Unit admission

Three studies explicitly reported Intensive Care Unit (ICU) admission rates after surgery.[18,21,23] Meta-analysis did not reveal any significant difference between groups (OR 0.61, 95% CI 0.24 to 1.53, P=0.29, **eFigure 3**), with no heterogeneity ($P_{heterogeneity}$=0.55, I^2=0%).

Surgical site infections

All eight RCTs documented surgical site infection rates,[18,19,20,21,22,23,24,25] however one combined reporting of surgical site infections with urinary tract infections and therefore could not be included in this pooled analysis.[19] Surgical site infection data for the trial by Mulrooney *et al.* was abstracted from the systematic review by Herbert *et al.*[6] Herbert *et al.* reported corresponding with Mulrooney *et al.* to obtain this additional information.

The seven RCTs that explicitly reported surgical site infections enrolled 625 patients. Patients who received an early oral protein-containing diet were significantly less likely to experience a surgical site infection (OR 0.39, 95% CI 0.21 to 0.71, *P*=0.002, **Figure 3**), with no important heterogeneity ($P_{heterogeneity}$=0.19, I^2=32%).

Anastomotic leak/dehiscence

Five RCTs enrolling 439 patients reported anastomotic leak,[18,21] anastomotic leak/dehiscence,[22,25] or anastomotic breakdown.[23] None of these trials reported using explicit and objective criteria to diagnose a leak/dehiscence/breakdown. Anastomotic leak/dehiscence data for the trial by Mulrooney *et al.* was abstracted from the systematic review by Herbert *et al.*[6] Herbert *et al.* reported corresponding with Mulrooney *et al.* to obtain this additional information.

Meta-analysis did not find any significant difference between groups (OR 0.74, 95% CI 0.30 to 1.87, *P*=0.53, **eFigure 4**) and no important heterogeneity was detected ($P_{heterogeneity}$=0.10, I^2=49%).

Postoperative nausea and vomiting

Three studies reported nausea.[18,20,25] Using a Likert scale, Lau *et al.* reported a significantly lower nausea score in the early diet containing protein group compared to the traditional group (2.5 early vs. 4.7, *P*=0.01).[20] However, Stewart *et al.* failed to find a significant difference between groups using a visual-analogue nausea scale (29 early vs. 31, reported as Not Significant[NS]),[25] and Beier-Holgersen *et al.* also failed to find a significant difference between groups in the incidence of nausea (19/30 early vs. 22/30, NS).[18] Due to the different measures used to assess nausea, pooled analysis could not be undertaken.

Three RCTs reported the number of patients who vomited,[18,20,25] two RCTs reported the number of patients with 'nausea and vomiting' combined,[19,21] and one study provided a graphical representation of

vomiting on each study day but did not explicitly report rates.[23]

Pooled analysis of the five RCTs enrolling 312 patients that explicitly reported rates demonstrated a significant reduction in postoperative nausea and vomiting attributable to the provision of an early oral protein-containing diet (OR 0.62, 95% CI 0.38 to 0.99, *P*=0.04, e**Figure 5**), with no important heterogeneity ($P_{heterogeneity}$=0.17, I^2=37%).

Pneumonia

Six RCTs enrolling 585 patients reported pneumonia.[18,20,22,23,24,25] Pneumonia data for the trials by Mulrooney *et al.* and Stewart *et al.* was abstracted from the systematic review by Herbert *et al.*[6] Herbert *et al.* reported corresponding with Mulrooney *et al.* and Stewart *et al.* to obtain this additional information.

Pooled analysis failed to demonstrate a significant difference between groups (OR 0.73, 95% CI 0.32 to 1.66, *P*=0.45, **eFigure 6**), with no heterogeneity ($P_{heterogeneity}$=0.60, I^2=0%).

Need for re-operation

Three RCTs enrolling 204 patients explicitly reported need for reoperation.[18,20,21] Pooled analysis failed to demonstrate a significant difference between groups (OR 0.49, 95% CI 0.16 to 1.51, *P*=0.22, **eFigure 7**), with no heterogeneity ($P_{heterogeneity}$=0.84, I^2=0%).

Intra-abdominal abscess/peritonitis

Six RCTs reported intra-abdominal abscess/peritonitis.[18,20,21,22,23,24] Data for the trial by Mulrooney *et al.* was abstracted from the systematic review by Herbert *et al.*[6] Herbert *et al.* reported corresponding with Mulrooney *et al.* to obtain this additional information.

Pooled analysis of these six RCTs enrolling 545 patients demonstrated a significant reduction in the onset of intra-abdominal abscess/peritonitis in patients who received an early oral protein-containing diet (OR 0.20, 95% CI 0.06 to 0.66, *P*=0.008, **eFigure 8**), with no heterogeneity ($P_{heterogeneity}$=0.98, I^2=0%).

Number of patients with serious postoperative complications

Six RCTs enrolling 552 patients explicitly reported the total number of patients in each study group who had at least one serious postoperative complication.[18,20,21,23,24,25] Serious postoperative complications included acute myocardial infarction, anastomotic leak/dehiscence, unexpected return to surgery, hospital

readmission within 30 days of discharge, surgical site infection, peritonitis, intestinal obstruction, and other postoperative infections. Because mortality served as the primary outcome for this study, it was not included in this analysis of serious postoperative complications.

Pooled analysis of these six RCTs revealed that the provision of an early oral protein-containing diet resulted in significantly fewer patients developing a serious postoperative complication (OR 0.60, 95% CI 0.40 to 0.89, P=0.01, **eFigure 9**). Despite reporting of a different subset of serious postoperative complications by each study, there was no important heterogeneity ($P_{heterogeneity}$=0.25, I^2=25%).

Number of patients with a postoperative infection

Four RCTs enrolling 210 patients reported the number of patients who had at least one postoperative infection.[18,19,21,24] Based on pooled analysis of these four RCTs, the provision of an early oral protein-containing diet resulted in a significant reduction in the number of patients who experienced a postoperative infection (OR 0.17, 95% CI 0.08 to 0.37, *P*<0.0001, **eFigure 10**), with no heterogeneity ($P_{heterogeneity}$=0.83, I^2=0%).

Sensitivity analysis

Focused on the primary outcome, the sensitivity analysis considered trials with *less certainty* regarding protein content of the intervention group's early nutrition. Thirteen clinical trials enrolling 1,216 patients were identified for inclusion in the sensitivity analysis.

These RCTs described their early nutrition intervention as "water",[26] "5% glucose",[27,28] "clear liquid",[29,30] "allowed to drink",[31] "oral liquids",[32] an "oral liquid diet",[33] a "fluid diet",[34] "fluids",[35] a "liquid diet",[36] a "semi-fluid diet",[37] or "filtrate liquids".[38]

Inclusion of these 13 RCTs in a sensitivity analysis failed to find an impact of early *non-protein liquid diets* on mortality (OR 1.01, 95% CI 0.29 to 3.51, *P*=0.99). Furthermore, there was important heterogeneity *between* RCTs that evaluated a *protein-containing diet* and RCTs that evaluated *non-protein liquid diets*, suggesting these different interventions have different effects on mortality ($P_{heterogeneity}$=0.14, I^2=54.7%, **Figure 4**).

Heterogeneity and stratified analysis

The only statistically significant result demonstrating important heterogeneity was the analysis of duration of hospital stay (I^2=75%, e**Figure 2**). Stratified analysis based on study intervention (enteral nutrition/solid diet/protein drink supplement) meaningfully reduced heterogeneity within each strata (**eFigure 11**). Interpretation of results within each strata revealed that early enteral nutrition did not have

any effect on duration of hospital stay (1.05 days, 95% CI -0.077 to 2.87 days, P=0.26, I^2=0%), whilst both an early solid protein-containing diet (-1.86 days, 95% CI -2.73 to -1.00, P<0.000001, I^2=35%) and early use of protein drink supplements (-3.54 days, 95% CI -4.59 to -2.49, P<0.000001, I^2=0%) significantly reduced duration of hospital stay.

Discussion

This systematic review identified eight RCTs that evaluated the impact of an early oral protein-containing diet on outcomes after elective lower gastrointestinal tract surgery in adults. Compared to later (traditional) feeding, resumption of an oral protein-containing diet before the end of POD 1 significantly reduced mortality, surgical site infection rate, postoperative nausea and vomiting, serious postoperative complications and other key measures of recovery after surgery. Furthermore, sensitivity analysis evaluating the early resumption of a *non-protein liquid diet* failed to find any effect on mortality.

Mitochondrial biogenesis and recovery from abdominal surgery

Surgery to the lower gastrointestinal tract results in local tissue injury at the site of the external incision and also compromises gut barrier function, even with only mild intestinal handling.[39,40] As a result of increased gut permeability, bacterial translocation occurs and initiates a systemic inflammatory response.[41,42,43,44] Systemic inflammation arising from low-grade endotoxemia is known to impair mitochondrial function leading to a measurable reduction in energy production capacity.[45] Mitochondrial dysfunction can depress protein synthesis [46] and impair immune response.[47]

Mitochondrial biogenesis is the process of growth and replication undertaken by mitochondria in response to an increased need for energy production during metabolic stress.[48] Serial muscle biopsies obtained from critically ill patients suggest that mitochondrial biogenesis may confer a survival advantage from critical illness by compensating for mitochondrial dysfunction and allowing increased energy demands to be met.[49]

Amino acids are accepted to stimulate mitochondrial biogenesis by activating the mammalian target of rapamycin (mTOR) pathway.[46,50,51] The direct effect of early protein intake on the active up-regulation of mitochondrial biogenesis provides a plausible mechanism of action to explain the survival advantage, and other important outcome benefits, demonstrated in this meta-analysis.[49]

Anastomotic leak

Anastomotic leak is one of the most serious adverse events after colorectal surgery.[52,53] Animal models demonstrate that initiating a protein-containing diet immediately after abdominal surgery significantly

increases the *strength* of an ileal or colorectal anastomosis.[54] Although our meta-analysis failed to find a significant reduction in the number of patients experiencing an anastomotic leak **(eFigure 4)**, we did identify a significant reduction in the number of patients experiencing intra-abdominal abscess/peritonitis **(eFigure 8)**. Based on the severity grading scheme proposed by Rahbari *et al*.,[52] a reduction in intra-abdominal abscess/peritonitis suggests that an early oral diet containing protein may have reduced the *severity* (Grade B or C) of anastomotic leaks. We strongly recommend that future trials in this field use pre-defined explicit criteria to objectively diagnose and grade the severity of anastomotic leaks.

Duration of hospital stay

Due to the presence of substantial and important heterogeneity in the assessment of duration of hospital stay, pooled analysis of this outcome may be misleading.[17] Heterogeneity between trials can arise for a number of reasons, including real differences in the study intervention, patient populations and/or the severity/stage of disease studied by each trial. The purpose of stratified (grouped) analyses is to investigate these potential sources of important heterogeneity.[17]

When studies were stratified (grouped) based on intervention (enteral feeding tube vs. solid diet vs. protein drink supplement), we found that duration of hospital stay was significantly reduced by receiving an early solid diet or protein drink supplement, with no heterogeneity within each strata (**eFigure 11**). However, since a number of stratified analyses were undertaken, these results should be viewed as hypothesis generating. We strongly recommend that future meta-analyses conduct assessments of duration of hospital stay stratified by intervention and interpret their results *within* each strata.

The role of early nutrition in enhanced recovery after surgery programs

Early nutrition is considered to be an essential component of enhanced recovery after surgery (ERAS) programs.[55] Striking recent data from a 911 patient observational study demonstrates that after undergoing colorectal cancer surgery in an ERAS program, delivery of nutrition on the day of operation was a strong independent predictor of 5-year postoperative survival.[56] This study does report that a significant number of patients received ‘nutritional supplements’ on the day of surgery, but it does not record whether these supplements contained protein thus, unfortunately, early protein intake was not completely assessed. Based on the results of our sensitivity analysis (**Figure 4**), we found a mortality benefit of early protein intake, not early calories alone. Small observational studies have demonstrated that higher early protein intake by ERAS patients undergoing elective colorectal surgery is associated with a shorter duration of hospital stay.[57] Future studies in this field need to ensure that the effects of early protein intake are assessed more thoroughly.

Which patients benefit the most?

It is intuitively appealing to attempt to identify individual patients who are most likely to benefit from an early oral protein-containing diet after elective lower gastrointestinal tract surgery. For example, if we could prove that patients who receive open operative procedures for malignant disease benefit most, we could focus our efforts on these patients. Unfortunately, the included clinical trials do not report outcomes by identifiable patient subgroups such as nutritional status, type of procedure or specific underlying disease. However, because the analysis of our primary outcome (mortality) does not demonstrate any heterogeneity ($P_{heterogeneity}$=0.95, I^2=0%) it supports the conclusion that there is no one subgroup of patients who benefit more than any other and that all patients included in this meta-analysis are likely to benefit in a similar fashion. Likewise, even though each clinical trial enrolled a different patient population who received different surgical procedures for different inciting causes, a lack of statistical heterogeneity supports the conclusion that the overall benefit from early oral protein diets are similar across all of these studies.

Strengths and limitations

The literature search supporting this systematic review was extensive and was not restricted by language of publication.[6] With the inclusion of eight RCTs recruiting 657 patients, the results of our meta-analysis are robust: significant benefits were demonstrated across multiple meaningful outcomes with no analysis suggesting any harm.

Whilst only one included RCT was identified as having a major methodological flaw leading to a potential high risk of bias,[25] all clinical trials in this field would benefit from improved reporting. Authors of RCTs should always report sufficient details regarding randomization such that the reader is assured that allocation concealment was maintained. Furthermore, outcomes should be reported on all patients randomized into an RCT and, finally, although blinding of a study intervention is not always feasible, blinded outcome assessment and adjudication is always possible. The most recent CONSORT Statement serves as an excellent guide with regards to the minimum standards for reporting an RCT.[58]

We did not assess time to first flatus, duration of ileus or time to first stool movement as we are unaware of any studies validating their use as surrogate measures for clinically meaningful outcomes.[59] Furthermore, we are unaware of any evidence-based statements from authoritative bodies or societies that make recommendations for their continued use to guide decisions to withhold nutrition from surgical patients.[1]

Finally, it is important to note that the clinical trials included in this meta-analysis did not set out to determine the amount of protein that should be targeted over the first few postoperative days to achieve maximum benefit. Each of the included trials was pragmatic, and attempted to achieve *any* protein intake during the first 24 h post-op. As in the real world, patients may refuse oral intake during the first 24 hours.

Due to the pragmatic nature of these trials, patients who refused oral intake were still included in the intention to treat analysis. Thus, the benefits established by these clinical trials are very likely to be achieved in the real world. Additional research is required to determine whether higher targets may benefit patients more.

Conclusions

This first systematic review focused exclusively on the effects of an early oral protein-containing diet versus later (traditional) feeding following elective lower gastrointestinal tract surgery found eight RCTs that addressed this clinical question. Meta-analysis of these eight RCTs demonstrated a significant reduction in mortality, and improvements in other key important outcomes, arising from an early oral protein-containing diet, with no indications of any harms. Furthermore, none of our analyses found any benefits in favor of later (traditional) feeding. Our results support a *Grade A recommendation* for an oral protein-containing diet to be initiated before the end of POD 1 after lower gastrointestinal surgery. If it is felt a *clear liquid* is clinically indicated, it is important to understand that *protein-containing clear liquid supplements are widely available*.

List Of Abbreviations

CNKI, China National Knowledge Infrastructure; **EORTC**, European Organization for Research and Treatment of Cancer.

Declarations

Ethics and approval

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article, its supplementary information files and the primary randomized controlled trials cited for inclusion.

Competing interests

Drs Pu, Heighes, Simpson, Wang, Hugh and Ms Liang reported no funding conflicts. **Dr Doig** reported receiving academic research grants related to nutrition in critical illness from the Australian National Health and Medical Research Council, Fresenius Kabi Deutschland GmbH and Baxter Healthcare Pty Ltd and speakers honoraria from Fresenius Kabi Deutschland GmbH, Baxter Healthcare Australia, Pty Ltd, Nestle Healthcare, Vevy, Switzerland and Nutricia Pharmaceutical (Wuxi) Co., Ltd. China. **Dr Wischmeyer** reported receiving grant funding related to Improving Nutrition Delivery in Acute Illness from the National Institute of Health National Heart, Lung, and Blood Institute R34 HL109369, Canadian Institutes of Health Research, Baxter, Fresenius, Lyric Pharmaceuticals, Isomark, Inc, and Medtronics. He served as a consultant on Improving Nutrition Care in Intensive Care Unit (ICU) and Perioperative Medicine to Nestle, Abbott, Fresenius, Baxter, Medtronics, Nutricia, and Lyric Pharmaceuticals, and Takeda for research related to this work. He received honoraria or travel expenses for lectures on improving nutrition care in illness from Abbott, Fresenius, and Medtronics.

Funding

The conduct of this study was not funded by any source.

Authors' Contributions

GSD conceived and designed the study, managed the project, conducted the statistical analysis, interpreted the results and helped draft the manuscript. **GSD** had full access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. **HP** and **PTH** contributed to study design, managed the project, participated in the critical appraisal of the literature, interpreted the results and helped draft the manuscript. **FS**, **YW**, **ZL** and **PW** participated in the study design and critical appraisal of the literature, interpreted the results, and contributed significantly towards critical revisions of the manuscript. **TJH** interpreted the results and contributed significantly towards critical revisions of the manuscript.

Gordon S Doig PhD (Epidemiology and Biostatistics) was responsible for and conducted all analyses. He had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgements

Not applicable.

Reference

1. Wischmeyer PE, Carli F, Evans DC et al. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Nutrition Screening and Therapy Within a Surgical

Enhanced Recovery Pathway. Anesthesia & Analgesia 2018;126(6):1883-1895.

2. Lewis SJ, Egger M, Sylvester PA, Thomas S. Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. BMJ 2001;323(7316):773-776.
3. Osland E, Yunus RM, Khan S, Memon MA. Early versus traditional postoperative feeding in patients undergoing resectional gastrointestinal surgery: a meta-analysis. JPEN J Parenter Enteral Nutr 2011;35(4):473-487.
4. Smeets BJJ, Peters EG, Horsten ECJ et al. Effect of Early vs Late Start of Oral Intake on Anastomotic Leakage Following Elective Lower Intestinal Surgery: A Systematic Review. Nutr Clin Pract 2018;33(6):803-812.
5. Lewis SJ, Andersen HK, Thomas S. Early Enteral Nutrition Within 24 h of Intestinal Surgery Versus Later Commencement of Feeding: A Systematic review and Meta-analysis. J Gastrointest Surg 2009;13:569-575.
6. Herbert G, Perry R, Andersen HK et al. Early enteral nutrition within 24 hours of lower gastrointestinal surgery versus later commencement for length of hospital stay and postoperative complications. Cochrane Database Syst Rev 2019;7:CD004080.
7. Doig GS, Heighes PT, Simpson F, Sweetman EA. Early enteral nutrition reduces mortality in trauma patients requiring intensive care: a meta-analysis of randomised controlled trials. Injury 2011;42(1):50-56.
8. Pu H, Doig GS, Heighes PT, Allingstrup MJ. Early Enteral Nutrition Reduces Mortality and Improves Other Key Outcomes in Patients With Major Burn Injury: A Meta-Analysis of Randomized Controlled Trials. Crit Care Med 2018;46(12):2036-2042.
9. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
10. Pu H, Heighes PT, Simpson F, Doig GS. Early post-operative enteral or oral nutrition for patients receiving lower gastrointestinal tract surgery: Methods for a meta-analysis of randomized controlled trials. Sydney: EvidenceBased.net; 2019.
11. Cochrane Handbook for Systematic Reviews of Interventions. 5.1.0 ed. The Cochrane Collaboration; 2011.
12. Graf J, Doig GS, Cook DJ, Vincent JL, Sibbald WJ. Randomized, controlled clinical trials in sepsis: has methodological quality improved over time? Crit Care Med 2002;30(2):461-472.
13. Bradburn MJ, Deeks JJ, Berlin JA, Russell LA. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med 2007;26(1):53-77.
14. Villar J, Mackey ME, Carroli G, Donner A. Meta-analyses in systematic reviews of randomized controlled trials in perinatal medicine: comparison of fixed and random effects models. Stat Med 2001;20(23):3635-3647.
15. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539-1558.

16. Hatala R, Keitz S, Wyer P, Guyatt G. Tips for learners of evidence-based medicine: 4. Assessing heterogeneity of primary studies in systematic reviews and whether to combine their results. CMAJ 2005;172(5):661-665.
17. Glasziou PP, Sanders SL. Investigating causes of heterogeneity in systematic reviews. Stat Med 2002;21(11):1503-1511.
18. Beier-Holgersen R, Boesby S. Influence of postoperative enteral nutrition on postsurgical infections. Gut 1996;39(6):833-835.
19. Carr CS, Ling KDE, Boulos P, Singer M. Randomised trial of safety and efficacy of immediate postoperative enteral feeding in patients undergoing gastrointestinal resection. BMJ 1996;312(7035):869-871.
20. Lau C, Phillips E, Bresee C, Fleshner P. Early use of low residue diet is superior to clear liquid diet after elective colorectal surgery: a randomized controlled trial. Ann Surg 2014;260(4):641-647.
21. Minig L, Biffi R, Zanagnolo V et al. Early oral versus "traditional" postoperative feeding in gynecologic oncology patients undergoing intestinal resection: a randomized controlled trial. Ann Surg Oncol 2009;16(6):1660-1668.
22. Mulrooney LJ, Bagley JS, Wilkinson JA, Kelty C, Coker AO, Jacog G. Nasojejunal feeding does not improve clinical outcomes and is poorly tolerated following colorectal surgery. Proc Nutrition Soc 2005;64:9A.
23. Ortiz H, Armendariz P, Yarnoz C. Is early postoperative feeding feasible in elective colon and rectal surgery? Int J Colorectal Dis 1996;11(3):119-121.
24. Shen H. Effect of early EN on the improvement of nutrition indexes and recovery of gastrointestinal function of posoperative patients with colon cancer. Qilu Nursing Journal 2013;19(21):28-30.
25. Stewart BT, Woods RJ, Collopy BT, Fink RJ, Mackay JR, Keck JO. Early feeding after elective open colorectal resections: a prospective randomized trial. Aust N Z J Surg 1998;68(2):125-128.
26. Wang Z, Shong B, Xiang J, Zhou Y, Wang D. Effect of early oral enteral nutrition on clinical outcomes after colorectal cancer surgery. Chin J Gastrointest Surg 2013;16(8):735-738.
27. Cao A. Application of early intestinal nutrition after colon and rectal cancer. Today Nurse 2009;9:42-43.
28. Li Y, Wu X, Luo W, Zhang M, Huang X, Wu L. The study of clinical application of early postoperative enteral nutrition after colorectalectomy. West China Medical Journal 2006;21(1):26-27.
29. Reissman P, Teoh TA, Cohen SM, Weiss EG, Nogueras JJ, Wexner SD. Is early oral feeding safe after elective colorectal surgery? A prospective randomized trial. Ann Surg 1995;222(1):73-77.
30. Pragatheeswarane M, Muthukumarassamy R, Kadambari D, Kate V. Early oral feeding vs. traditional feeding in patients undergoing elective open bowel surgery-a randomized controlled trial. J Gastrointest Surg 2014;18(5):1017-1023.
31. Feo CV, Romanini B, Sortini D et al. Early oral feeding after colorectal resection: a randomized controlled study. ANZ J Surg 2004;74(5):298-301.

32. Chatterjee S, Bala SK, Chakraborty P et al. A comparative study between early enteral feeding (within 24 hours) versus conventional enteral feeding after enteric anastomosis. Bangladesh Journal of Medical Science 2012;11(4):273-283.
33. da Fonseca LM, Profeta da Luz MM, Lacerda-Filho A, Correia MI, Gomes da SR. A simplified rehabilitation program for patients undergoing elective colonic surgery--randomized controlled clinical trial. Int J Colorectal Dis 2011;26(5):609-616.
34. Dag A, Colak T, Turkmenoglu O, Gundogdu R, Aydin S. A randomized controlled trial evaluating early versus traditional oral feeding after colorectal surgery. Clinics (Sao Paulo) 2011;66(12):2001-2005.
35. El NA, Fikry A, El MT et al. Early oral feeding in patients undergoing elective colonic anastomosis. Int J Surg 2009;7(3):206-209.
36. Hartsell PA, Frazee RC, Harrison JB, Smith RW. Early postoperative feeding after elective colorectal surgery. Arch Surg 1997;132(5):518-520.
37. Lee TG, Kang SB, Kim DW, Hong S, Heo SC, Park KJ. Comparison of early mobilization and diet rehabilitation program with conventional care after laparoscopic colon surgery: a prospective randomized controlled trial. Dis Colon Rectum 2011;54(1):21-28.
38. Nematihonar B, Salimi S, Noorian V, Samsami M. Early Versus Delayed (Traditional) Postoperative Oral Feeding in Patients Undergoing Colorectal Anastomosis. Adv Biomed Res 2018;7:30.:30.
39. Alazawi W, Pirmadjid N, Lahiri R, Bhattacharya S. Inflammatory and Immune Responses to Surgery and Their Clinical Impact. Ann Surg 2016;264(1):73-80.
40. Anup R, Aparna V, Pulimood A, Balasubramanian KA. Surgical stress and the small intestine: role of oxygen free radicals. Surgery 1999;125(5):560-569.
41. Reddy BS, Gatt M, Sowdi R, MacFie J. Surgical manipulation of the large intestine increases bacterial translocation in patients undergoing elective colorectal surgery. Colorectal Dis 2006;8(7):596-600.
42. Qiao Z, Li Z, Li J, Lu L, Lv Y, Li J. Bacterial translocation and change in intestinal permeability in patients after abdominal surgery. J Huazhong Univ Sci Technolog Med Sci 2009;29(4):486-491.
43. Takesue Y, Ohge H, Uemura K et al. Bacterial translocation in patients with Crohn's disease undergoing surgery. Dis Colon Rectum 2002;45(12):1665-1671.
44. MacFie J, Reddy BS, Gatt M, Jain PK, Sowdi R, Mitchell CJ. Bacterial translocation studied in 927 patients over 13 years. Br J Surg 2006;93(1):87-93.
45. Vico TA, Marchini T, Ginart S et al. Mitochondrial bioenergetics links inflammation and cardiac contractility in endotoxemia. Basic Res Cardiol 2019;114(5):38-0745.
46. Morita M, Gravel SP, Hulea L et al. mTOR coordinates protein synthesis, mitochondrial activity and proliferation. Cell Cycle 2015;14(4):473-480.
47. West AP. Mitochondrial dysfunction as a trigger of innate immune responses and inflammation. Toxicology 2017;391:54-63.
48. Holloszy JO. Regulation of mitochondrial biogenesis and GLUT4 expression by exercise. Compr Physiol 2011;1(2):921-940.

49. Carre JE, Orban JC, Re L et al. Survival in critical illness is associated with early activation of mitochondrial biogenesis. Am J Respir Crit Care Med 2010;182(6):745-751.
50. Dann SG, Thomas G. The amino acid sensitive TOR pathway from yeast to mammals. FEBS Lett 2006;580(12):2821-2829.
51. Cao Y, Liu S, Liu K, Abbasi IHR, Cai C, Yao J. Molecular mechanisms relating to amino acid regulation of protein synthesis. Nutr Res Rev 2019;1-9.
52. Rahbari NN, Weitz J, Hohenberger W et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery 2010;147(3):339-351.
53. Daams F, Wu Z, Lahaye MJ, Jeekel J, Lange JF. Prediction and diagnosis of colorectal anastomotic leakage: A systematic review of literature. World J Gastrointest Surg 2014;6(2):14-26.
54. Moss G, Greenstein A, Levy S, Bierenbaum A. Maintenance of GI function after bowel surgery and immediate enteral full nutrition. I. Doubling of canine colorectal anastomotic bursting pressure and intestinal wound mature collagen content. JPEN J Parenter Enteral Nutr 1980;4(6):535-538.
55. Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review. JAMA Surg 2017;152(3):292-298.
56. Gustafsson UO, Oppelstrup H, Thorell A, Nygren J, Ljungqvist O. Adherence to the ERAS protocol is Associated with 5-Year Survival After Colorectal Cancer Surgery: A Retrospective Cohort Study. World J Surg 2016;40(7):1741-1747.
57. Yeung SE, Hilkewich L, Gillis C, Heine JA, Fenton TR. Protein intakes are associated with reduced length of stay: a comparison between Enhanced Recovery After Surgery (ERAS) and conventional care after elective colorectal surgery. Am J Clin Nutr 2017;106(1):44-51.
58. Moher D, Hopewell S, Schulz KF et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg 2012;10(1):28-55.
59. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med 1989;8(4):431-440.

Figures

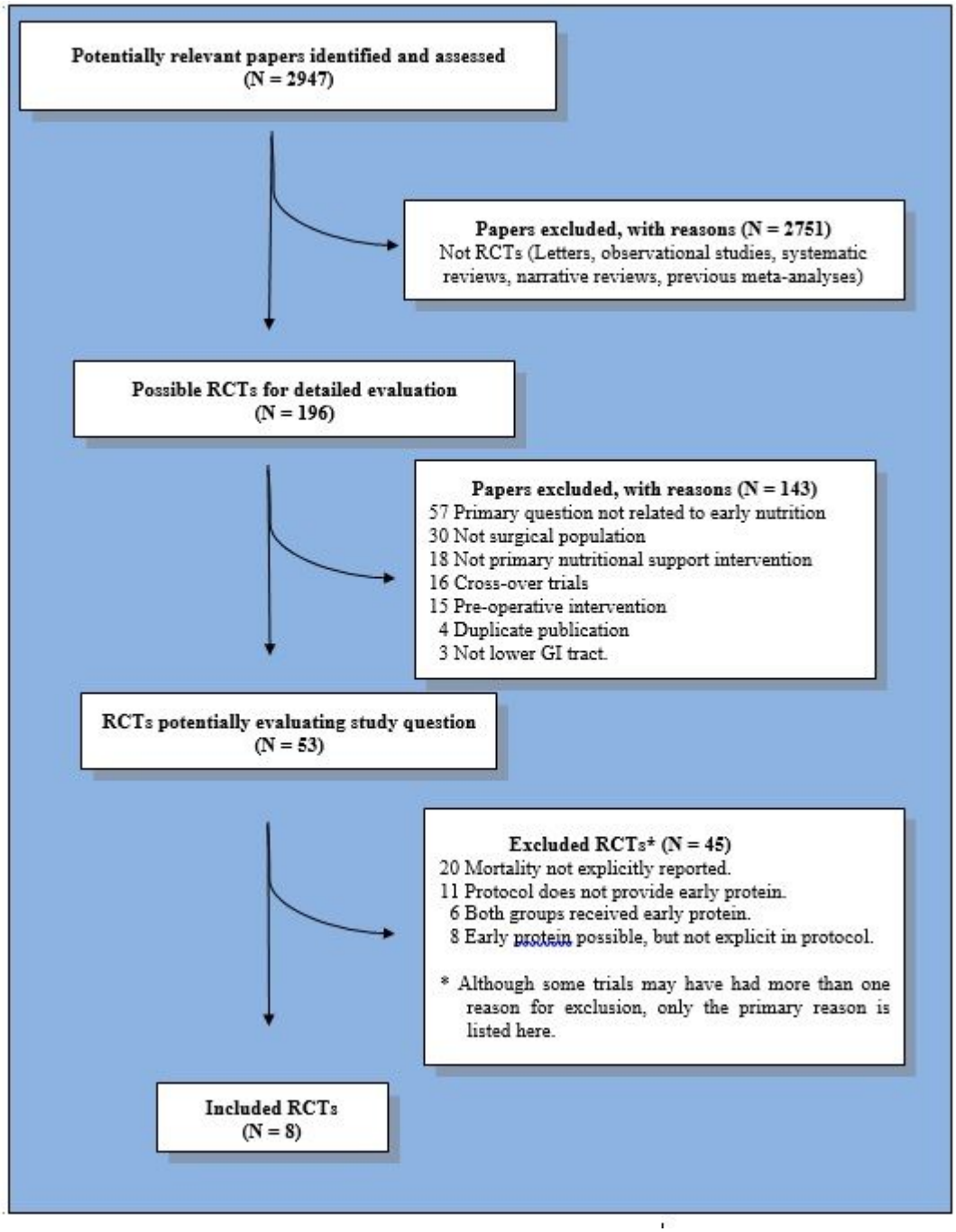

Figure 1

Flow diagram of the study selection process Legend: N: number, RCT: randomized controlled trial, GI: gastrointestinal

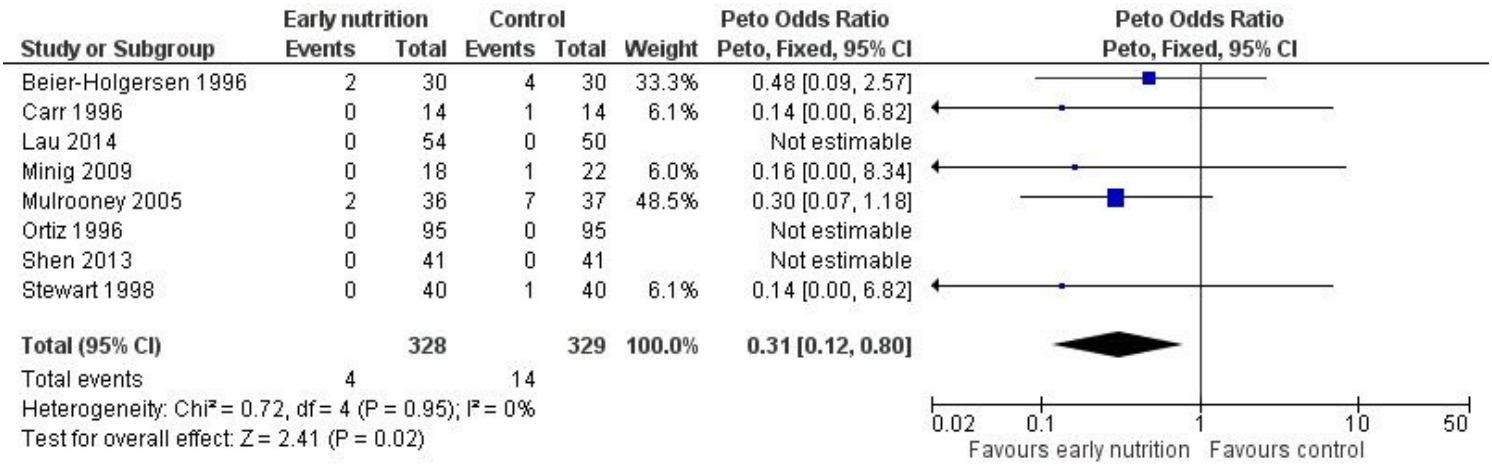

Figure 2

Analysis of primary outcome, mortality Legend: CI: confidence interval

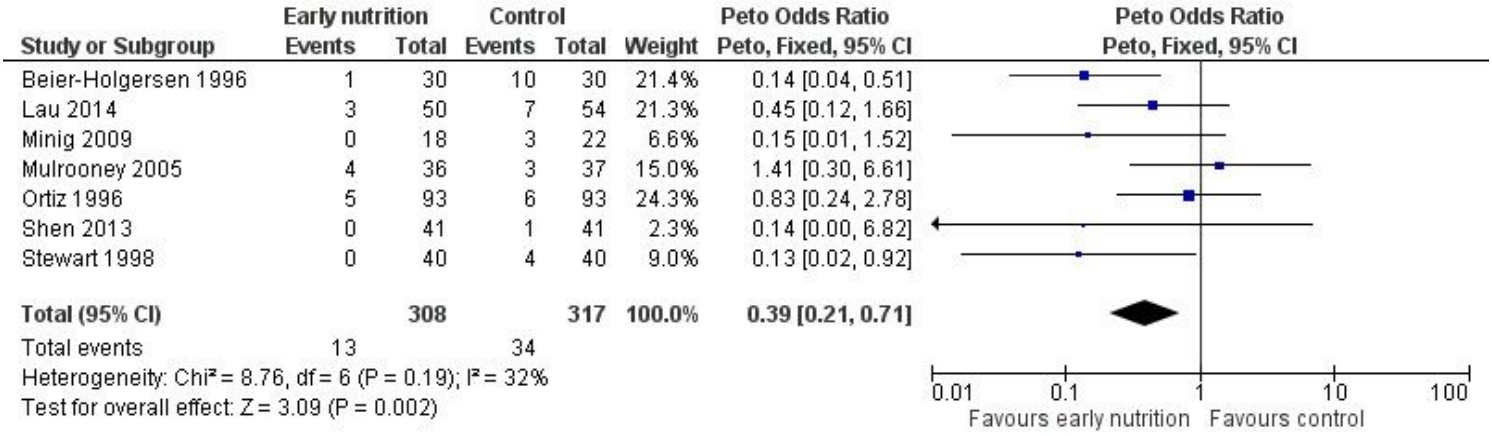

Figure 3

Number of patients with a surgical site infection Legend: CI: confidence interval

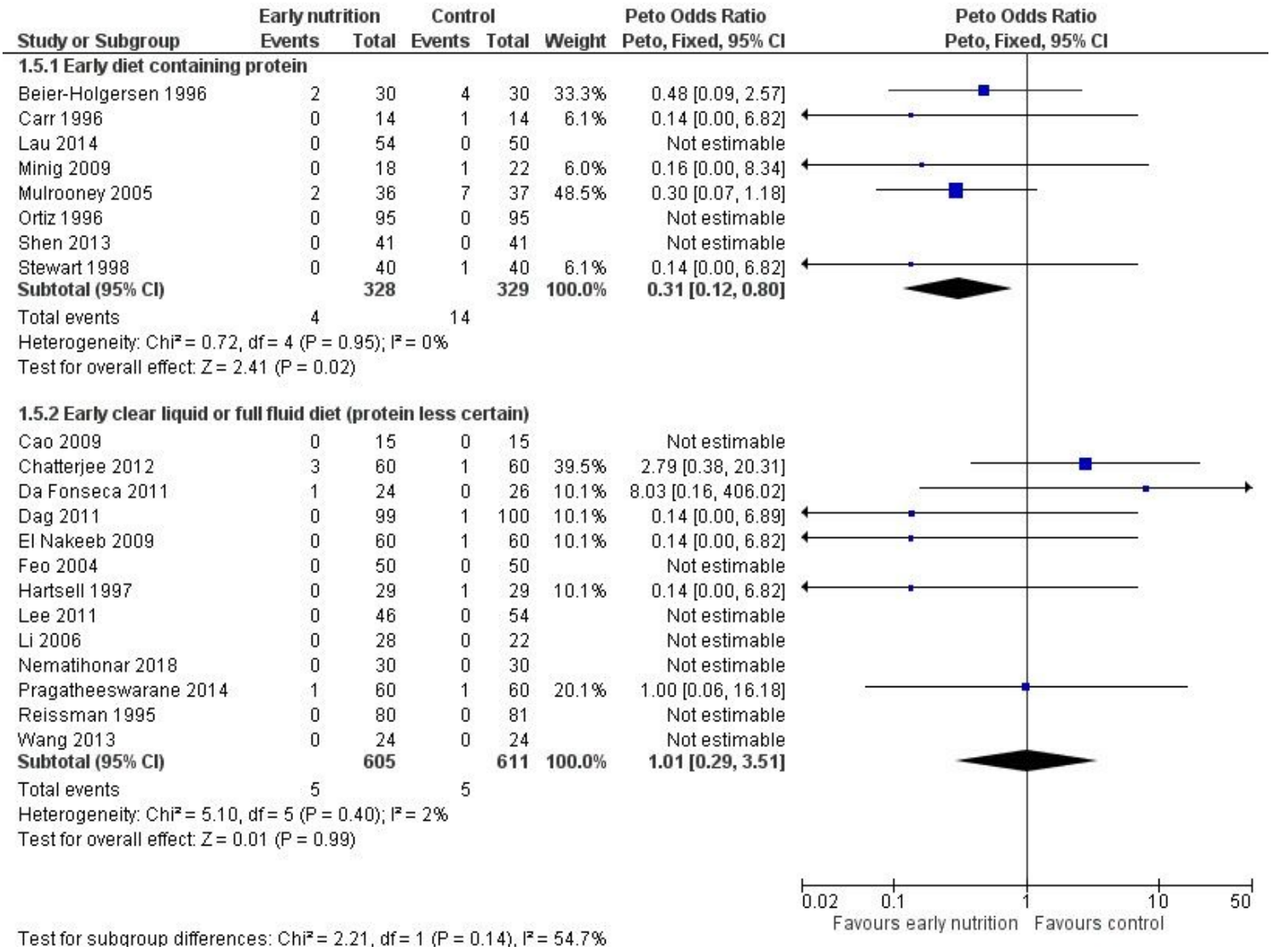

Figure 4

Sensitivity Analysis: Trials with less certainty regarding protein content Legend: CI: confidence interval

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- MethodsforEarlyENMASx.pdf
- PRISMA2009checklist1.doc
- OnLineSupplementEarlyNutritionSx2020Ver20.pdf