The efficacy of fiber-supplemented enteral nutrition in critically ill patients: a systematic review and meta-analysis of randomized controlled trials with trial sequential analysis

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Critical Care

REVIEW

Open Access

The efficacy of fiber-supplemented enteral nutrition in critically ill patients: a systematic review and meta-analysis of randomized controlled trials with trial sequential analysis

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Abstract

Background Evidence on the benefits of fiber-supplemented enteral nutrition (EN) in critically ill patients is inconsistent, and critical care nutrition guidelines lack recommendations based on high-quality evidence. This systematic review and meta-analysis (SRMA) aims to provide a current synthesis of the literature on this topic.

Methods For this SRMA of randomized controlled trials (RCT), electronic databases (MEDLINE, EMBASE, CENTRAL) were searched systematically from inception to January 2024 and updated in June 2024. Trials investigating clinical effects of fiber-supplemented EN versus placebo or usual care in adult critically ill patients were selected. Two independent reviewers extracted data and assessed the risk of bias of the included studies. Random-effect meta-analysis and trial sequential analysis (TSA) were conducted. The primary outcome was overall mortality, and one of the secondary outcomes was diarrhea incidence. Subgroup analyses were also performed for both outcomes.

Results Twenty studies with 1405 critically ill patients were included. In conventional meta-analysis, fiber-supplemented EN was associated with a significant reduction of overall mortality (RR 0.66, 95% CI 0.47, 0.92, $p=0.01$, $I^2=0\%$; 12 studies) and diarrhea incidence (RR 0.70, 95% CI 0.51, 0.96, $p=0.03$, $I^2=51\%$; 11 studies). However, both outcomes were assessed to have very serious risk of bias, and, according to TSA, a type-1 error cannot be ruled out. No subgroup differences were found for the primary outcome.

Conclusion Very low-certainty evidence suggests that fiber-supplemented EN has clinical benefits. High-quality multicenter RCTs with large sample sizes are needed to substantiate any firm recommendation for its routine use in this group of patients.

PROSPERO registration number: CRD42023492829.

Keywords Medical nutrition therapy, Fiber, Enteral nutrition, Critical care, Systematic review, Meta-analysis, Trial sequential analysis

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Introduction

Critical illness is frequently associated with severe changes in gut function, metabolism and induces a catabolic stress state, often leading to malnutrition and compromised immune function [1–3].

Enteral nutrition (EN) is the preferred route of medical nutrition therapy for critically ill patients [4]. However, a common challenge among critically ill patients is enteral feeding intolerance with a prevalence of up to 75% [5, 6], leading to inadequate nutrient delivery and gastrointestinal (GI) symptoms like constipation or diarrhea [7, 8]. Therefore, inexpensive and safe interventions would be needed to manage this challenge.

Dietary fiber (DF) is a type of carbohydrate that is not/only partially hydrolyzed or absorbed in the human small intestine [9]. DF has been shown to provide various benefits in disease prevention among healthy individuals, including, among other benefits, reduced risk of mortality, type-2 diabetes, and cardiovascular disease [10–13]. A recent narrative review suggested considerable benefits from DF in critically ill patients, attributed to its functions in maintaining gut barrier integrity, modulating immune responses, supporting the gut microbiome, and contributing to systemic anti-inflammatory responses [9]. Formulations containing DF have been introduced attempting to improve GI tolerance of EN in critically ill patients [14]. However, existing trials about DF for critically ill patients yield inconsistent results [13], and there is a lack of up-to-date, high-quality systematic reviews of randomized controlled trials (RCTs) with meta-analysis (SRMA). Consequently, the routine use of DF in intensive care unit (ICU) settings remains unclear. While the American Society for Parenteral and Enteral Nutrition (ASPEN) and the Society of Critical Care Medicine (SCCM) recommend considering the routine use of fermentable soluble DF supplements in stable medical and surgical ICU patients, they advise against the routine use of mixed soluble and insoluble DFs due to concerns about bowel ischemia and dysmotility [15]. Conversely, the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines do not address the use of DF in the ICU [16].

Prior systematic reviews examining the effects of fiber-supplemented EN in adult critically ill patients [17–19], have included non-RCTs [20–24]. Furthermore, none of the preceding meta-analyses applied trial sequential analysis (TSA), limiting accurate assessment of type-1 and –2 error within the meta-analyses [25]. TSA helps in assessing the robustness of results and minimizes the risk of distortion due to random errors [26].

Therefore, we conducted a SRMA of RCTs and included TSA to generate a higher quality and more precise estimate regarding the efficacy of fiber-supplemented EN in critically ill patients. We also performed GRADE certainty of evidence assessment, thereby enhancing the conclusiveness and reliability of our findings.

Methods

This SRMA was performed in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [27]. The PRISMA 2020 checklist is shown in Additional file 1: Part 1. The protocol was registered in PROSPERO (CRD42023492829).

Eligibility criteria

RCTs of adult (age ≥ 16 years) critically ill patients (defined as admission to the ICU, or if uncertain, a mortality rate of ≥ 5% in the control group or mechanical ventilation at the study inclusion) that compared fiber-supplemented EN with placebo or usual care and reported at least one clinical or GI outcome were included. Pseudorandomized trials and studies that investigated the effects of synbiotics were excluded. Studies among patients with elective or cancer surgery or studies only reporting laboratory, metabolic or nutritional outcomes were also excluded.

Outcomes

The primary outcome was overall mortality. When multiple mortality endpoints were reported in a trial, the data was included in the following order of preference: 28-/30-day mortality > hospital mortality > ICU mortality > other mortality. Secondary outcomes included diarrhea, other GI complications, ICU and hospital length of stay (LOS), duration of mechanical ventilation (MV), infectious complications, metabolic (blood glucose, triglycerides) and nutritional (e.g. tolerated feeding volumes, time to reach energy targets) outcomes.

Information sources and search strategies

MEDLINE, EMBASE, and CENTRAL (Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials) were searched through OVID on January 11, 2024, for all relevant RCTs published from database inception to January 09, 2024. No language restrictions were made. The reference lists of previous SRMAs were also reviewed and ClinicalTrials.gov was searched for ongoing studies. The detailed search strategies are presented in Additional file 1: Part 1. The search was repeated on June 10, 2024, to identify potential studies published after the initial search.

Study selection

Search results were exported into Covidence (Veritas Health Innovation, Melbourne, Australia) for screening

and removal of duplicates. The article titles and abstracts were screened by two independent reviewers (JK and AH). Full texts of potential eligible trials were retrieved and reviewed independently by the same two reviewers. Disagreements were discussed with a third author (ZYL).

Data collection

Data from eligible trials were extracted independently by two reviewers (JK and AH). Abstracted data including study and patient characteristics, funding sources, feeding information, clinical, metabolic and nutritional outcomes, diarrhea, and adverse events are summarized in Additional file 1: Tables S1–S7. For studies that reported median (Q1–Q3) for continuous outcomes, authors were contacted to obtain the mean and standard deviation (SD). If means and SDs were unavailable, those outcomes were excluded from the meta-analysis. No assumption or data conversion was made if the information could not be obtained.

Study quality and risk-of-bias assessment

The quality of the included trials was evaluated independently by two authors using the Canadian Critical Care Nutrition (CCN) Methodological Quality System (JK and ZYL) and the Cochrane Risk of Bias 2 tool (ROB2) (JK and ZYL) [28]. The overall ROB2 assessment was categorized as high risk-of-bias, some concerns, or low risk of bias. The risk of bias traffic light and summary plots were generated by the risk-of-bias visualization (robvis) tool [29]. The CCN Methodological Quality System is used in CCN systematic reviews and allows quality comparisons across topics and time [30]. The methodologic score ranges from 0 to 14 points, where a higher score indicates higher study quality.

Data analysis

All analyses were performed with a random effects model using RevMan 5.4 (Cochrane IMS, Oxford, UK). For dichotomized outcomes, the pooled risk ratio (RR) was estimated by the DerSimonian and Laird random effect meta-analysis. For continuous outcomes, the random effect mean difference (MD) was estimated. Heterogeneity was quantified by the I^2 measure. The result of the meta-analysis was presented in the forest plot generated by RevMan. Presence of potential publication bias was evaluated by funnel plots for overall outcomes. Egger's test for funnel plot asymmetry was performed by using the metafor package in RStudio (version 2023.12.1) if ≥ 10 studies were included in a meta-analysis [31]. All estimates were provided with 95% confidence intervals (CI). A p-value < 0.05 was considered statistically significant.

Subgroup analyses

Subgroup analyses were performed for overall mortality and diarrhea incidence. The following a priori subgroup analyses were conducted: (1) publication date before 2000 versus after 2000, (2a) fermentable versus non-fermentable versus mixed fiber, (2b) viscous versus non-viscous versus mixed fiber, (2c) soluble versus insoluble versus mixed fiber (based on the classification provided by Gill et al [10]), (3) daily fiber dose < 20 g versus ≥ 20 g, (4) average age < 50 years versus ≥ 50 years, (5) average APACHE II score < 17 versus ≥ 17, (6) medical versus surgical versus mixed ICU, (7) intervention start ≤ 24 h versus ≤ 48 h, and (8) minimum duration of intervention < 6 days versus ≥ 6 days. All cut-offs for continuous data were based on the median. The calculation of the daily fiber doses is detailed in Additional file, Table S12. For the age subgroup, an a priori planned cut-off of 65 years was adjusted to the median of 50 years post-hoc to provide a more even distribution of studies while maintaining validity for the comparison of younger versus older study population. Subgroup analyses were not performed for the following pre-planned domains as data were not sufficiently available: patients with abdominal surgery versus others, and patients with shock/vasopressor use versus others. Additionally, no subgroup analysis on study quality was conducted, as none of the included studies had a low risk of bias. The following post-hoc subgroup analyses were added: (9) Co-intervention with immunonutrition versus DF only, (10) funding source of the trial (industry vs. non-industry), and (11) standard formula versus non-standard formula in the control group. All results of the subgroup analyses were not adjusted for multiplicity. Hence, they should be viewed as hypothesis-generating.

Trial sequential analysis

To control for type-1 and type-2 errors [25], TSA was performed for the following outcomes: overall mortality, diarrhea incidence, ICU LOS and hospital LOS. All TSA were performed using the TSA software (0.9.5.10 Beta, The Copenhagen Trial Unit, Denmark) with the prespecified parameters detailed in Additional file 1: Part 1.

Certainty of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to rate the certainty of evidence for outcomes analyzed with TSA [32]. The certainty of the evidence was rated as high, moderate, low, and very low by considering the risk of bias, inconsistency, indirectness, imprecision, and

publication bias. GRADEpro was used to prepare the GRADE evidence profile table [33].

Deviations from the original protocol

While diarrhea was initially considered as secondary outcome alongside other GI complications in the original protocol, we decided to place particular emphasis on it in our analyses for two main reasons. First, diarrhea is a highly prevalent symptom associated with enteral nutrition, with prevalence rates up to 41%, and it significantly impacts patient dignity and morbidity, contributing to issues such as electrolyte imbalances and increased infection risk [34]. Additionally, the incidence of diarrhea was the second most frequently reported outcome in the included studies, after mortality, and provided substantially more data than other secondary outcomes.

Subgroup analyses were performed only for mortality and diarrhea incidence, which was not explicitly specified in the original protocol. This decision was made, as these outcomes were the most clinically relevant and had the most data available, thereby avoiding excessive analyses with limited data.

Results

Study selection

The search identified a total of 363 records from the databases. After removing duplicates, 236 abstracts were screened and of these, 44 full-text articles were assessed for eligibility. Twenty trials with a total of 1405 patients published between 1988 and 2021 were included. The detailed study selection flow is presented in Fig. 1. Five ongoing or unpublished related trials were identified (Additional file 1: Table S8). The excluded trials with the reason for exclusion are listed in Additional file 1: Table S9.

Risk of bias and study quality

The CCN score of the studies ranged from 2 to 10, with a median score of 6 (Additional file 1: Table S10). The ROB2 plots are presented in Additional file 1: Fig. S1. None of the included studies had an overall rating of low risk of bias. In 12 studies that reported mortality outcomes, 9/12 (75%) were at high risk of bias and 3/12 (25%) had some concerns. The biases mainly arose from the randomization process, deviations from intended interventions and selection of the reported results.

Study characteristics

Included studies and patient characteristics are summarized in Additional file 1: Table S1. The sample sizes ranged from 20 to 220 (median: 56). Only one study was a multi-center trial [35]. Seven studies enrolled mixed medical and surgical patients [35–41], three included only medical [42–44] and two included only surgical ICU patients [45, 46]. One study included trauma and septic patients with stress diabetes [47], two studies included patients with severe acute pancreatitis [48, 49], two included patients with multi-organ trauma [50, 51], one included patients with traumatic brain injury and hemorrhagic stroke [52], and diseases or ICU admission category were unclear in two studies [53, 54]. In all reviewed studies, EN was administered via feeding tubes. The majority (n = 16) compared fiber-supplemented EN with standard EN [36, 38–45, 48–54]. Two studies added immunomodulating components in the intervention group: one study included arginine and antioxidants (vitamins E and C) [35], and another added glutamine [51], while the control groups lacked these components. Conversely, two studies compared fiber-supplemented EN against control EN formulations that either contained glutamine, arginine, and linolenic acid [46] or were high in protein [46, 47]. The intervention groups in these studies did not receive these additional components. One study administered glutamine in both groups [37], and another provided high-protein formulas in both groups [35]. A detailed summary of the interventions is outlined in Additional file 1: Table S3, and all relevant outcomes are summarized in Additional file 1: Tables S4–S6.

Overall mortality

In statistically aggregated data from twelve studies, a significant effect of fiber-supplemented EN on overall mortality was observed (RR 0.66, 95% CI 0.47, 0.92, $p = 0.01$, $I^2 = 0\%$) (Fig. 2).

No evidence of funnel plot asymmetry was detected in the overall analysis ($p = 0.14$, Additional file 1: Fig. S9).

There was no evidence for subgroup differences in any of the subgroup analyses. The results of all subgroup analyses are summarized in Additional file 1: Table S11 and visualized in Additional file 1: Fig. S2.

Diarrhea

Fiber-supplemented EN was associated with a significant reduction of the diarrhea incidence (RR 0.70, 95% CI 0.51, 0.96, $p = 0.03$, $I^2 = 51\%$; 11 studies) (Fig. 3) and no evidence of funnel plot asymmetry was detected in the overall analysis ($p = 0.41$, Additional file 1: Fig. S10a).

Additionally, a significant benefit of fiber-supplemented EN in meta-analysis of diarrhea scores according to the Hart and Dobb diarrhea scale was found (MD -2.77, 95% CI −4.10, −1.45, $p < 0.0001$, $I^2 = 0\%$; 3 studies; Additional file 1: Fig. S4). Visual inspection of the funnel plot found no evidence of asymmetry (Additional file 1: Fig. S10b).

In the subgroup analyses, studies published after 2000 indicated a significant reduction of diarrhea events

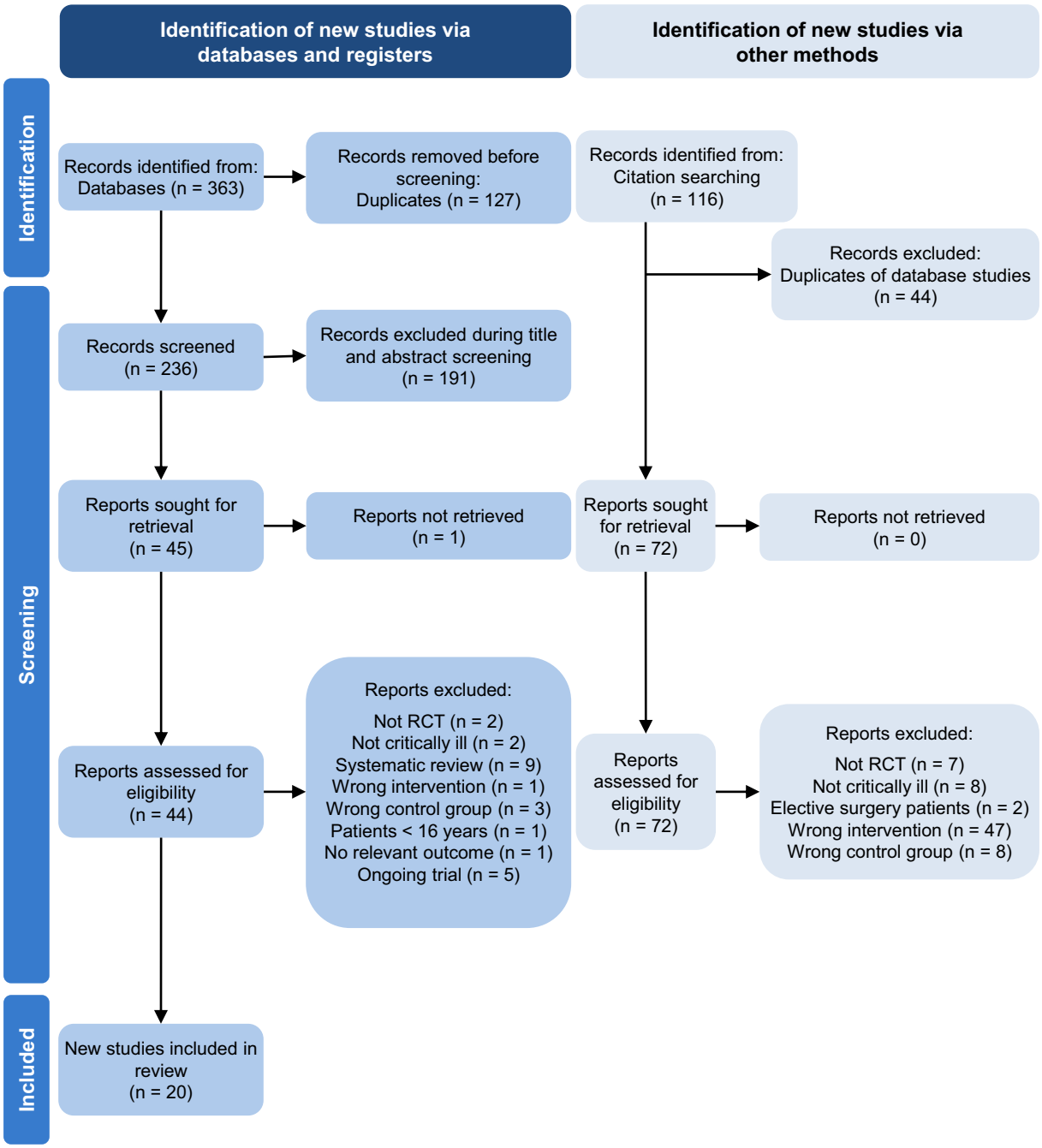

Fig. 1 PRISMA Flowchart. One report was not retrieved because neither the abstract nor the full text was available

through fiber-supplemented EN (RR 0.59, 95% CI 0.40, 0.85, $p = 0.005$, $I^2 = 43\%$; 9 studies), a result that was not supported by studies published before 2000 (RR 1.04, 95% CI 0.73, 1.46, $p = 0.84$, $I^2 = 0\%$; 2 studies) (test for subgroup differences: $p = 0.03$, $I^2 = 79.4\%$). Providing fiber-supplemented EN in sicker patients (APACHE II ≥ 17 compared to APACHE < 17 and unclear APACHE score) and in medical ICUs (compared to surgical ICUs, mixed ICUs and unclear admission type) seemed to be associated with a significant reduction of diarrhea incidence (tests for subgroup differences: $p = 0.01$ and $p = 0.02$, respectively). No evidence for subgroup differences was found in other subgroup analyses, as summarized in Additional file 1: Table S11 and visualized in Additional file 1: Fig. S3.

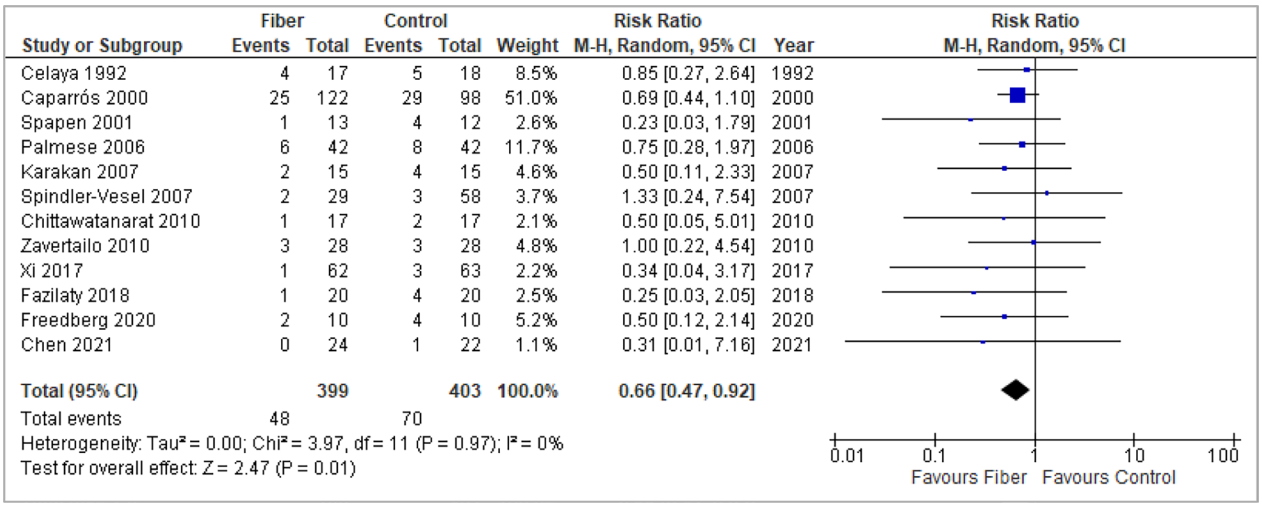

Fig. 2 Meta-analysis of overall mortality

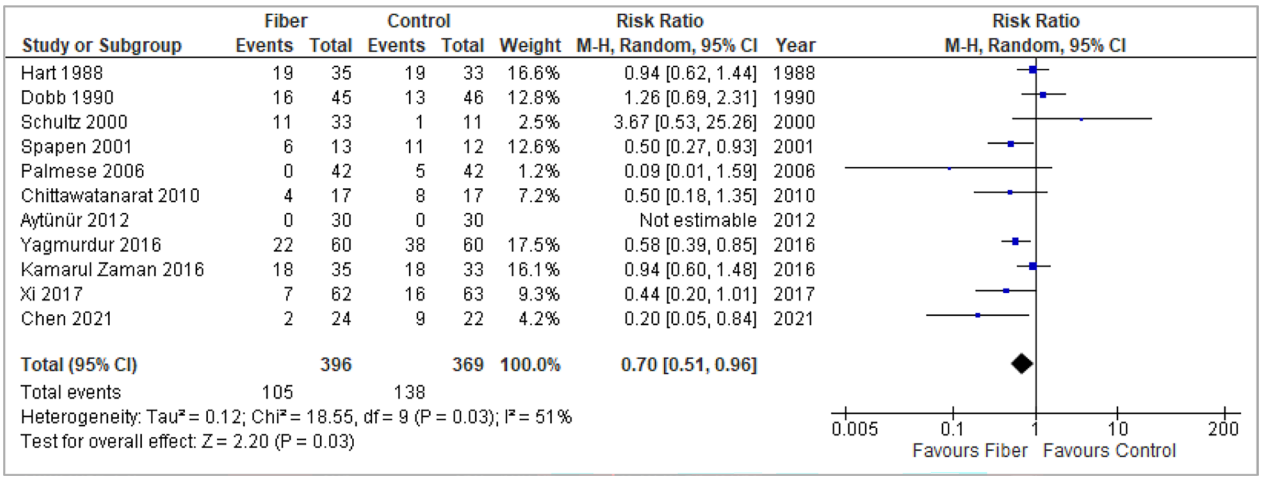

Fig. 3 Meta-analysis of diarrhea incidence

Other gastrointestinal complications

Four studies reported the overall incidence of GI complications (n = 315). No significant difference was found between groups (RR 0.75, 95% CI 0.49, 1.15, $p = 0.19$, $I^2 = 58\%$) (Additional file 1: Fig. S5a). There was also no significant difference between groups for the incidence of abdominal distension, vomiting, regurgitation and GI bleeding (Additional file 1: Fig. S5b–S5e). However, pooled data from six studies showed a significant benefit of fiber-supplemented EN for the incidence of constipation (RR 0.33, 95% CI 0.19, 0.58, $p = 0.0001$, $I^2 = 0\%$) (Additional file 1: Fig. S5f). Visual inspection of the funnel plots found no evidence of asymmetry (Additional file 1: Fig. S11).

Length of ICU and hospital stay

Fiber-supplemented EN was associated with a significantly reduced ICU (MD -3.62, 95% CI −6.24, −1.00, $p = 0.007$, $I^2 = 39\%$; 6 studies) and hospital LOS (MD −7.51, 95% CI −12.41, −2.61, $p = 0.003$, $I^2 = 0\%$; 3 studies) (Fig. 4). Visual inspection of the funnel plots found no evidence of asymmetry (Additional file 1: Fig. S12 and S13).

Infectious complications

No association was observed between fiber-supplemented EN and the overall incidence of infectious complications (RR 0.65, 95% CI 0.37, 1.14, $p = 0.13$, $I^2 = 0\%$; 3 studies) (Additional file 1: Fig. S6a). There was no

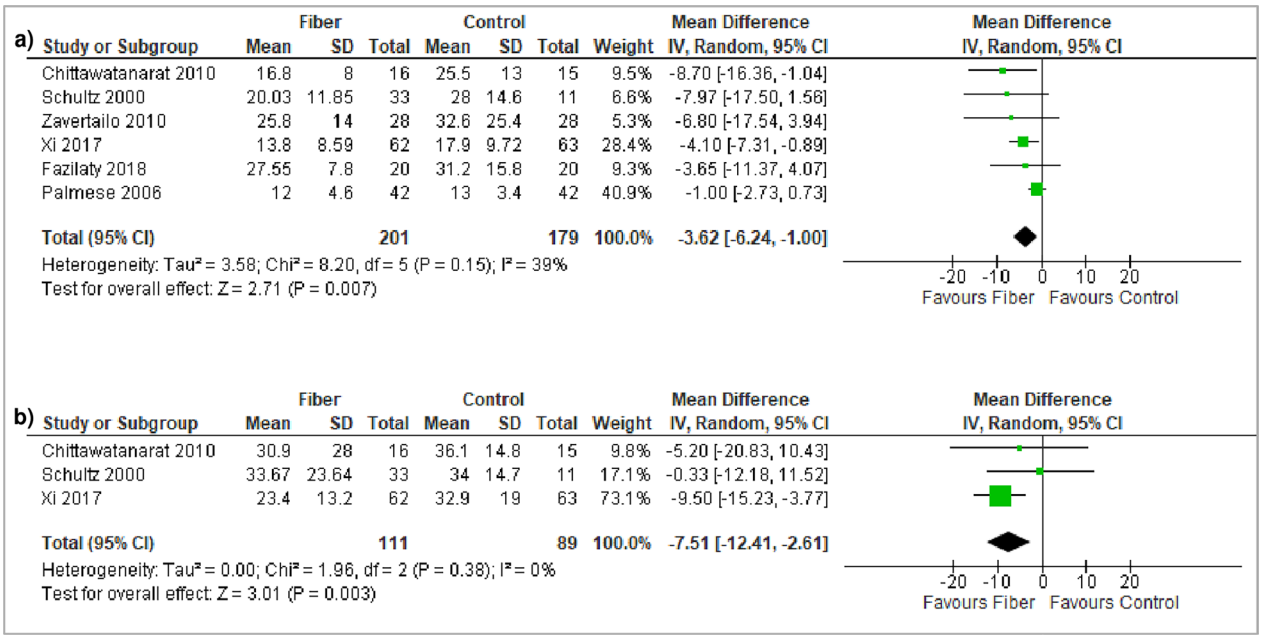

Fig. 4 Meta-analysis of **a** ICU LOS and **b** Hospital LOS

significant evidence for influence on the incidence of pneumonia, urinary tract infection, intra-abdominal infection, sepsis, vascular infection, wound infection and bacteremia (Additional file 1: Fig. S6b–S6h). Visual inspection of the funnel plots found no evidence of asymmetry (Additional file 1: Fig. S14).

Duration of mechanical ventilation

In three studies reporting the duration of MV, there was no significant difference between groups (MD 0.02, 95% CI −2.30, 2.34, $p=0.98$, $I^2=39\%$) (Additional file 1: Fig. S7) and visual inspection of the funnel plot found no evidence of asymmetry (Additional file 1: Fig. S15).

Metabolic outcomes

One study reported episodes of hypoglycemia, finding a significant benefit of fiber-supplemented EN [54]. Two studies presented blood glucose [47, 48] and one study serum triglyceride levels [47] (Additional file 1: Table S5). Due to heterogeneous timing and units of measurement, the data were unsuitable for a pooled meta-analysis.

Nutritional outcomes

Gastric residual volume, assessed in three studies, showed no significant differences at various timepoints [44, 46, 53]. Five studies [35, 36, 48, 50, 52] measured the administered caloric intake, with one indicating a benefit for fiber supplementation on the mean overall energy intake [48] and one on the intake on specific days [52]. Tolerated feeding volumes were investigated in five studies [38–40, 44, 46], with one revealing significantly greater volumes for the intervention group on specific days [40] and one for the mean daily volume ratio [44] (Additional file 1: Table S5). Due to variability in timing and units of measurement, data was not aggregated for these outcomes.

For meta-analysis, the time to reach energy targets was pooled from two studies, revealing a beneficial effect of fiber-supplemented EN (MD −2.25, 95% CI −4.16, −0.33, $p=0.02$, $I^2=53\%$) (Additional file 1: Fig. S8). Visual inspection of the funnel plot found no evidence of asymmetry (Additional file 1: Fig. S16).

Adverse events

Three studies reported the incidence of adverse events, but they were not pooled due to inconsistency in definitions. One study investigated GI adverse events and observed no significant difference between groups [51]. Another study found no differences between groups for the incidence or severity of adverse health events [42]. One study found no adverse events related to DF but did not provide a specific definition and did not compare these findings to the control group [48] (Additional file 1: Table S7).

Trial sequential analysis

Results of TSA are summarized in Table 1 and presented in Fig. 5 and Additional file 1: Fig. S17–S19. TSA revealed that the current systematic review did not achieve the required information size (RIS) to detect

Table 1 Summary of results of TSA

Effect size	Incidence, or variance	I^2 (%)	D^2 (%)	RIS	% of RIS attained	Pooled effect (TSA adjusted 95% CI)	Z-curve passed the conventional boundaries?	Z-curve passed the TSA boundaries?	Z-curve passed the futility boundaries?
Overall mortality (12 studies, n = 802)									
RRR: 10.0%	17.4%	0	0	19,155	4.19	NA	Yes	No	No
RRR: 20.0%*	17.4%	0	0	4584	17.5	0.66 (0.17, 2.55)	Yes	No	No
RRR: 30.0%*	17.4%	0	0	1944	41.3	0.66 (0.38, 1.14)	Yes	No	No
Intensive care unit length of stay (6 studies, n = 380)									
MIREDIF 1 day	51.1	39	69.9	7119	18.7	− 3.62 (− 14.30, 7.06)	Yes	No	No
MIREDIF 2 days*	51.1	39	69.9	1781	21.3	− 3.62 (− 9.80, 2.56)	Yes	No	No
MIREDIF 3 days*	51.1	39	69.9	792	48.0	− 3.62 (− 7.73, 0.49)	Yes	No	No
Hospital length of stay (3 studies, n = 200)									
MIREDIF 1 day	312.2	0	0	13,122	1.5	NA	Yes	No	No
MIREDIF 2 days*	312.2	0	0	3281	3.1	− 7.51 (− 27.50, 12.48)	Yes	No	No
MIREDIF 3 days*	312.2	0	0	1459	13.7	− 7.51 (− 27.50, 12.48)	Yes	No	No
Diarrhea incidence (11 studies, n = 765)									
RRR: 15.0%*	37.4	51	60.5	7644	10.0	0.70 (0.20, 2.49)	Yes	No	No
RRR: 25.0%	37.4	51	60.5	2678	28.6	0.70 (0.38, 1.29)	Yes	No	No
RRR: 35.0%*	37.4	51	60.5	1325	57.7	0.70 (0.45, 1.09)	Yes	No	No

TSA trial sequential analysis, I^2 Between-trial heterogeneity, D^2 diversity-estimate, *RRR* relative risk reduction, *MIREDIF* minimally relevant difference, *RIS* required information size, *NA* not applicable, *CI* confidence interval

*Post-hoc sensitivity analyses

the pre-specified effect sizes for overall mortality, diarrhea incidence, ICU and hospital LOS. In addition, for all outcomes, the pooled RR crossed the boundaries of conventional meta-analysis (i.e. significant) but did not cross (i.e. not significant) the trial sequential boundaries or the futility boundaries. This suggests the possibility of false positive results, indicating that more adequately designed studies are required to accrue sufficient information to confirm any benefits and justify the routine use of fiber-supplemented EN in critically ill patients. Post-hoc, additional plausible larger effect sizes were tested, and the interpretations were similar (Table 1).

GRADE certainty of the evidence

The overall certainty of evidence using GRADE was rated as very low for all examined outcomes, implicating that the true effect is likely to be substantially different from the estimated effect (Table 2). The level of evidence was mainly downgraded due to very serious risk of bias and serious imprecision.

Discussion

Summary of main findings

Overall, this SRMA of 20 RCTs found very low-certainty evidence suggesting the benefits of fiber-supplemented EN in critically ill patients. Although the latter indicated a potential improvement in clinical and diarrheal

(See figure on next page.)

Fig. 5 Trial Sequential Analysis (TSA) for overall mortality. **a** RRR = 10%, **b** RRR = 20%, **c** RRR = 30%. *DARIS* diversity-adjusted required information size; *RRR* relative risk reduction. The Z curve in blue measures the treatment effect (pooled relative risk). The parallel lines in green are the boundaries of conventional meta-analysis (alpha 5%). The red lines, located outside the parallel lines, are the boundaries of benefit and harm. These are boundaries of conventional meta-analysis adjusted for between-trial heterogeneity and multiple statistical testing (TSA boundaries). A treatment effect outside the TSA boundaries of benefit/harm indicates reliable evidence for a pre-defined magnitude of treatment effect, and a treatment effect within the futility zone (the triangle between the parallel lines) indicates that there is reliable evidence of an absence of a pre-defined magnitude of treatment effect

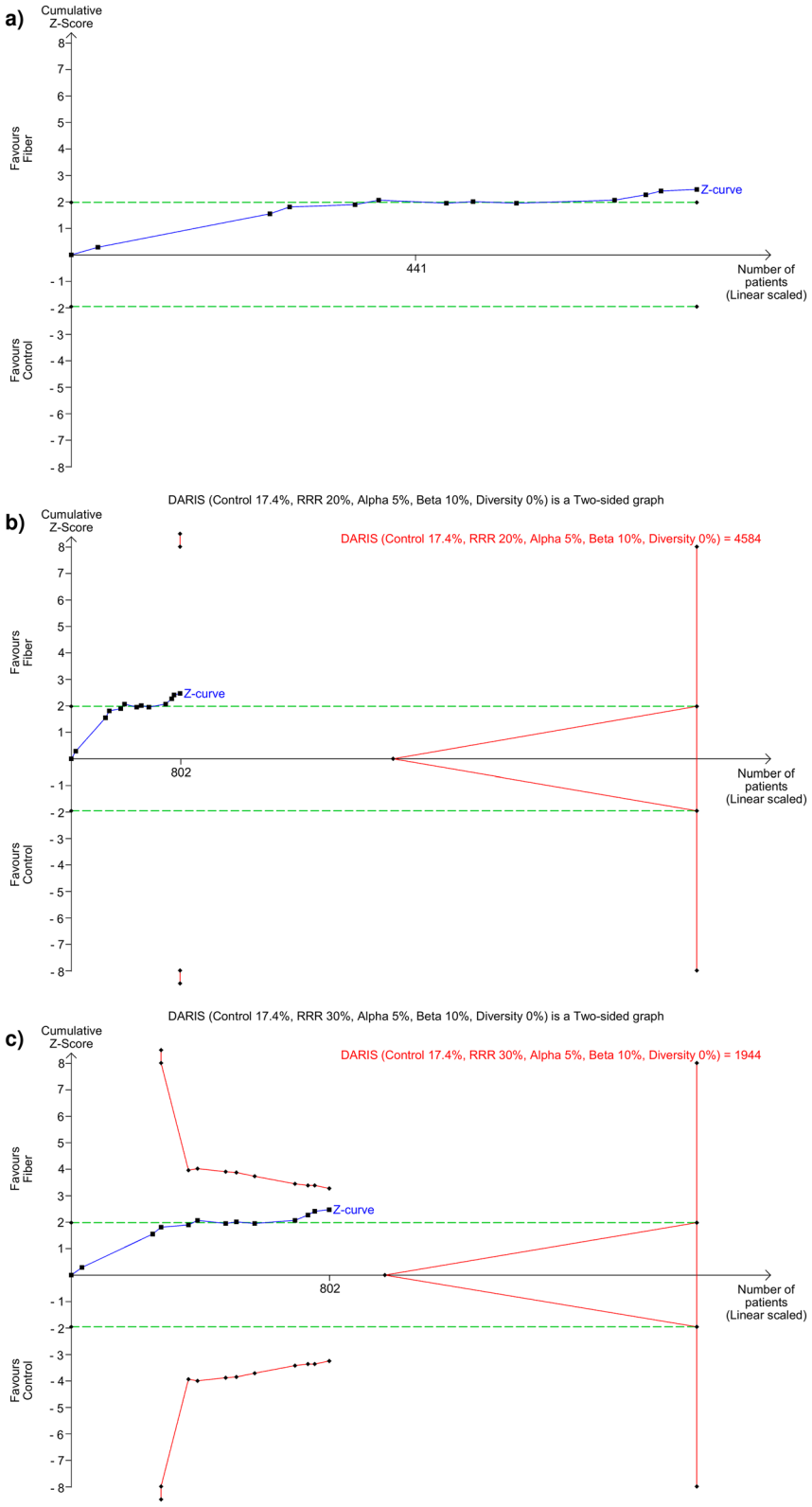

Fig. 5 (See legend on previous page.)

Table 2 GRADE certainty assessment and summary of findings table

Certainty assessment							Summary of findings				
Participants (studies) follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With control	With fiber		Risk with control	Risk difference with fiber
Overall mortality											
802 (12 RCTs)	Very serious[a]	Not serious	Not serious	Serious[b]	None	⊕◯◯◯ Very low	70/403 (17.4%)	48/399 (12.0%)	RR 0.66 (0.47, 0.92)	174 per 1000	59 fewer per 1000 (from 92 to 14 fewer)
Diarrhea incidence											
765 (11 RCTs)	Very serious[c]	Serious[d]	Not serious	Serious[b]	None	⊕◯◯◯ Very low	138/369 (37.4%)	105/396 (26.5%)	RR 0.70 (0.51, 0.96)	374 per 1000	112 fewer per 1000 (from 183 to 15 fewer)
ICU LOS											
380 (6 RCTs)	Very serious[e]	Not serious	Not serious	Serious[b]	None	⊕◯◯◯ Very low	179	201	–	The mean ICU LOS was 0	MD 3.62 lower (6.24 lower to 1 lower)
Hospital LOS											
200 (3 RCTs)	Very serious[f]	Not serious	Not serious	Serious[b]	None	⊕◯◯◯ Very low	89	111	–	The mean hospital LOS was 0	MD 7.51 lower (12.41 lower to 2.61 lower)

CI confidence interval, *MD* mean difference, *RR* risk ratio

[a] 3/12 studies had some concerns and 9/12 studies had high risk of bias

[b] Wide trial sequential analysis adjusted confidence interval

[c] 1/11 studies had some concerns and 10/11 studies had high risk of bias

[d] The overall heterogeneity is $I^2 = 51\%$

[e] 1/6 studies had some concerns and 5/6 studies had high risk of bias

[f] All included trials had high risk of bias

outcomes, TSA suggested that the accrued information size is insufficient, and more trials are needed to confirm these benefits. Furthermore, the overall certainty of evidence was compromised by a serious risk of bias in the trials.

Interpretation of the results in the context of other evidence

One SRMA by Cara et al. in 2021 assessed the safety of EN with DF based on 19 studies, including RCTs, retrospective cohort studies, case reports and case series [17]. They found no significant effects on diarrheal events, other GI complications, mortality, or ICU and hospital LOS.

Another SRMA by Liu et al. from 2022 included 20 RCTs and one cohort study, investigating interventions with fiber, probiotics or synbiotics. Liu et al. revealed no significant impact of DF on all clinical outcomes in fiber-only studies [18].

The most recent SRMA from the same group from 2023 included 13 RCTs [19], although one of the included studies was a pseudorandomized trial [55]. They concluded that DF might (or might not) reduce mortality, diarrhea, other GI complications, ICU and hospital LOS and the time to reach full EN.

Given our meticulous search strategy, which was significantly more thorough in both scope and detail, we were able to include a larger number of RCTs than previous SRMAs [36, 37, 47, 50, 52, 53]. Nevertheless, all studies were of low quality and the information size is insufficient to draw definitive conclusions regarding the benefits (or harms) of fiber-supplemented EN.

Impact of the results on clinical practice and future research

The complexity of clinical decision-making regarding the routine administration of DF in critically ill patients is reflected by the absence of clear guidance in major nutritional guidelines. ESPEN guidelines do not address the use of DF in the ICU at all [16]. In contrast, ASPEN recommends caution with the use of insoluble fiber [15] due to historical concerns about bowel obstruction, a potential adverse event documented in two case reports from 1990 that investigated five surgical and trauma patients receiving insoluble fiber [23, 24]. The studies in our meta-analyses are small and of low quality, and adverse effects of DF, especially bowel obstruction, were rarely reported outcomes. This is making it difficult to confirm or dismiss ASPEN's cautious approach.

Generally, classifying fiber only by its solubility is increasingly recognized as outdated, and recent expert opinion papers highlight the importance of considering additional physicochemical characteristics such as viscosity and fermentability [9, 10]. A nuanced understanding of fiber's properties and biological mechanisms could further inform the design of future clinical trials, increasing the possibility of detecting a true clinically significant benefit and potential adverse effects.

Most importantly, our GRADE assessments implicate that the true effect of fiber-supplemented EN is likely to be substantially different from the estimated effect. The TSA results suggest that the findings of our meta-analyses may be at risk of type-1 errors, and more robust studies are needed to validate whether a real difference exists. The high risk of bias among the included studies underscores the potential for overestimation of benefits. Overall, given the very low-certainty of evidence, no strong recommendations can be made regarding the routine use of fiber-supplemented EN in critically ill patients. Although diarrhea is a common and relevant symptom in critically ill patients and fiber-supplemented EN is relatively inexpensive, its potential benefits should be approached with caution. Given the potential type-1 errors and overestimations of effect, the possibility that DF could even be harmful cannot be excluded. Therefore, high-quality RCTs are needed to accumulate sufficient evidence and substantiate the efficacy and safety of fiber-supplemented EN. Until such evidence is available, clinicians should consider individual patient circumstances when deciding on the use of DF supplementation.

The results of our TSA further suggest that future trials should not be powered for mortality unless the expected effect size is large (e.g. a RRR of 30%), a magnitude more commonly observed in pharmaceutical trials. Instead, future studies should be powered for diarrhea incidence due to its high prevalence among critically ill patients and because the required sample size is relatively more achievable compared to the other outcomes.

Strengths and limitations

Our SRMA has numerous strengths. We conducted a meticulous systematic search and performed robust quality and GRADE assessments. In addition, the meta-analysis of accurately selected RCTs enhances the overall quality of evidence of our SRMA compared to previous SRMAs. Including non-RCTs in a meta-analysis can lead to reduced reliability due to higher susceptibility to biases, increased methodological variability, and higher heterogeneity [26]. Finally, our SRMA is the first to explore the effects of fiber-supplemented EN through TSA, allowing us to estimate the required sample size for future trials. Overall, our SRMA provides the highest quality of evidence available on fiber-supplemented EN in critically ill patients.

Our SRMA also faces important limitations. Firstly, the studies included were predominantly single-centered and

all had small sample sizes. None of the studies had a low risk of bias and most had a high risk of bias, which can lead to overestimations of benefits and underestimations of harm. Secondly, despite our efforts to obtain missing data from the authors, not all studies could be aggregated in the statistical analyses due to the diverse ways outcomes were measured and reported. For most outcomes, fewer than ten studies provided data for the meta-analysis, resulting in low patient numbers. Thirdly, as we excluded trials that only reported on metabolic or nutritional outcomes, our analysis provides an incomplete view of the evidence regarding these outcomes. Finally, in most subgroup analyses, not all studies from the overall analyses could be categorized into a defined subgroup due to missing data on subgroup characteristics. We also observed an uneven distribution of studies and population sizes across most of the subgroup analyses. Generally, the validity of our subgroup analyses is very low due to the very low certainty of evidence characterizing the overall results, which limits the interpretability and significance of these findings. Also, the multiplicity of subgroup analyses was not corrected for, and the findings from these analyses should be considered hypothesis-generating rather than confirmatory. Nonetheless, our subgroup analyses suggest several areas for future trials on tailored enteral nutrition, including the optimal type, dosage, start timing, and treatment duration of DF, as well as the patient populations that benefit most from DF supplementation.

Conclusion

This SRMA with TSA shows very low-certainty evidence suggesting that fiber-supplemented EN has clinical benefits, and future trials should explore diarrheal incidence as a primary outcome. Overall, given the very low-certainty of evidence, current findings should not be considered definitive to guide clinical practice. Large-scale, high-quality RCTs are required to accumulate sufficient evidence to justify recommendations for the routine use of fiber-supplemented EN in critically ill patients. Additionally, the optimal DF type, dosage, start timing, and treatment duration, as well as the critically ill patient population that benefits the most from fiber-supplemented EN should be explored.

Abbreviations

ASPEN	American Society for Parenteral and Enteral Nutrition
CCN	Critical care nutrition
D^2	Diversity estimate
DARIS	Diversity adjusted required information size
DF	Dietary fiber
EN	Enteral nutrition
ESPEN	European Society for Clinical Nutrition and Metabolism
ICU	Intensive care unit
LOS	Length of stay
MD	Mean difference
MIREDIF	Minimally relevant difference
MV	Mechanical ventilation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
RIS	Required information size
ROB2	Cochrane Risk of Bias 2
RR	Risk ratio
RRR	Relative risk reduction
SCCM	Society of Critical Care Medicine
SD	Standard deviation
TSA	Trial sequential analysis

Supplementary Information

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Supplementary Material 1.

Author contributions

All authors contributed to the conception and design of this review. JLK, AH and ZYL performed the literature search, data extraction, and quality assessment. JLK, AH, ZYL and CCHL contributed to the data analysis. JLK generated the summary tables and figures. JLK, AH, ZYL, CCHL, CS and DKH interpreted the data. The manuscript was drafted by JLK. All authors provided critical revisions and approved the final manuscript.

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Availability of data and materials

All generated data are presented within the manuscript or the additional file.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

AH holds a research stipend from the Medical Faculty RWTH Aachen ("Habilitationsstipendium"), grants for IITs from the German Research Foundation, the Lotte and John Hecht Memorial Foundation, Fresenius Kabi, Pascoe Pharma and Baxter. She receives lecture fees and travel honoraria from Fresenius Kabi and Baxter. CS has served as consultant and received honorarium as speaker for Fresenius, BRAUN and Baxter. ED has received speaker honoraria from Baxter. None of the above mentioned are related to this specific systematic review. All other authors declare no competing interests.

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Publisher's Note

Additional file

The efficacy of fiber-supplemented enteral nutrition in critically ill patients: a systematic review and meta-analysis of randomized controlled trials with trial sequential analysis

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Table of contents

PART 1: Methods (additional description)

1. Search strategies

a) Embase Classic+Embase <1947 to 2024 January 09>

#	Query	Results from 11 Jan 2024
1	Critical illness/	36,387
2	Intensive care/	151,692
3	Artificial ventilation/	194,908
4	Invasive ventilation/	9,292
5	Invasive positive pressure ventilation/	99
6	Intensive care medicine/	1,643
7	Critically ill patient/	68,222
8	Intensive care unit/	236,159
9	Medical intensive care unit/	4,345
10	Surgical Intensive care unit/	2,935
11	Endotracheal intubation/	67,086
12	Multiple organ failure/	51,168
13	Sepsis/	211,264
14	Bacteremia/	54,074
15	Anaerobic bacteremia/	21
16	Catheter-related bacteremia/	106
17	Gram negative sepsis/	4,397
18	Gram positive sepsis/	69
19	Polymicrobial bacteremia/	28
20	Fungemia/	4,411
21	Candidemia/	5,518
22	Cryptococcemia/	22
23	Septic complication/	41
24	Sepsis-associated encephalopathy/	669
25	Sepsis-associated coagulopathy/	253
26	Sepsis-induced acute lung injury/	86
27	Sepsis-induced myocardial injury/	88
28	Septicemia/	24,466
29	Severe sepsis/	213
30	Urosepsis/	4,404
31	Hemorrhagic septicemia/	401
32	Endotoxemia/	12,461
33	shock/	43,744
34	Septic shock/	70,100
35	Toxic shock syndrome/	4,436
36	Endotoxic shock/	122
37	staphylococcal toxic shock syndrome/	43
38	streptococcal toxic shock syndrome/	179
39	capillary leak syndrome/	3,834
40	cardiogenic shock/	39,631
41	dengue shock syndrome/	559
42	hemorrhagic shock/	21,780
43	hypovolemic shock/	6,420
44	ischemic shock/	12
45	traumatic shock/	4,351
46	vasodilatory shock/	526
47	Systemic inflammatory response syndrome/	16,617
48	Hyperinflammatory syndrome/	377
49	Cytokine storm/	8,743
50	Cytokine release syndrome/	9,005
51	Adult respiratory distress syndrome/	57,372
52	Acute lung injury/	18,588
53	Transfusion related acute lung injury/	2,661

54	Severe acute respiratory syndrome/	11,639
55	Heart infarction/	343,148
56	Heart arrest/	95,583
57	cardiopulmonary arrest/	6,989
58	out of hospital cardiac arrest/	15,331
59	Extracorporeal oxygenation/	39,557
60	arterio-venous ECMO/	126
61	veno-arterial ECMO/	4,869
62	veno-venous ECMO/	3,419
63	Multiple trauma/	17,967
64	brain injury/	104,039
65	acquired brain injury/	2,830
66	brain concussion/	8,491
67	brain contusion/	4,704
68	brain damage/	48,276
69	brain stem injury/	2,959
70	cerebellum injury/	2,701
71	diffuse brain injury/	208
72	traumatic brain injury/	67,978
73	Acute liver failure/	11,894
74	Acute on chronic liver failure/	5,691
75	Fulminant hepatic failure/	2,536
76	Acute pancreatitis/	40,439
77	Acute hemorrhagic pancreatitis/	6,095
78	Hemorrhagic pancreatitis/	618
79	Acute kidney failure/	132,446
80	Continuous renal replacement therapy/	9,018
81	continuous hemodiafiltration/	2,761
82	continuous hemodiafiltration/	2,761
83	continuous hemodialysis/	1,713
84	continuous hemofiltration/	3,108
85	modified ultrafiltration/	280
86	slow continuous ultrafiltration/	120
87	intermittent renal replacement therapy/	120
88	Burn/	73,321
89	Burn shock/	702
90	Electric burn/	2,876
91	Burn unit/	3,287
92	critical care.mp.	76,744
93	intensive care.mp.	499,435
94	critical illness.mp.	45,368
95	critically ill.mp.	108,501
96	ICU.ti,ab,kw.	173,590
97	Mechanical*2 ventilat*3.ti,ab,kw.	116,741
98	intubat*3.ti,kw.	26,472
99	Sepsis.mp.	285,388
100	Septicemia.mp.	35,967
101	Septic shock.mp.	78,867
102	Shock.ti,ab,kw.	298,762
103	Multiple organ failure.ti,ab,kw.	12,493
104	Multiple organ dysfunction syndrome.ti,ab,kw.	3,852
105	MODS.ti,ab,kw.	3,908
106	Systemic inflammatory response syndrome.ti,ab,kw.	9,414
107	Acute respiratory distress syndrome.mp.	33,813
108	ARDS.ti,ab,kw.	33,137
109	Acute lung injury.ti,ab,kw.	25,550
110	Myocardial infarction.ti,ab,kw.	336,929
111	Cardiac arrest.ti,ab,kw.	75,336
112	Extracorporeal Membrane Oxygenation.ti,ab,kw.	26,316
113	ECMO.ti,ab,kw.	27,600
114	Multiple trauma.ti,ab,kw.	4,598
115	Polytrauma.ti,ab,kw.	6,472
116	Multitrauma.ti,ab,kw.	431

117	Brain injur*3.ti,ab,kw.	123,488
118	Traumatic brain injury.ti,ab,kw.	70,031
119	TBI.ti,ab,kw.	53,313
120	Acute Liver failure.ti,ab,kw.	14,286
121	Acute pancreatitis.ti,ab,kw.	43,792
122	Acute kidney injury.ti,ab,kw.	67,785
123	AKI.ti,ab,kw.	42,930
124	Continuous renal replacement therapy.ti,ab,kw.	6,656
125	CRRT.ti,ab,kw.	5,614
126	Sustained low efficiency dialysis.ti,ab,kw.	335
127	SLED.ti,ab,kw.	1,624
128	Intermittent h?emodialysis.ti,ab,kw.	2,638
129	Burn unit.ti,ab,kw.	2,104
130	Burn patient.ti,ab,kw.	1,725
131	dietary fiber/	27,476
132	prebiotic agent/	13,199
133	resistant starch/	653
134	arabinoxylan/	1,508
135	beta glucan/	7,356
136	cellulose/	46,566
137	dextrin/	2,462
138	guar gum/	3,640
139	Hemicellulose/	7,849
140	Inulin/	13,163
141	Pectin/	12,511
142	galactomannan/	4,815
143	fructose oligosaccharide/	3,036
144	galactose oligosaccharide/	1,399
145	Lignin/	19,805
146	methylcellulose/	8,896
147	alginic acid/	31,199
148	ispagula/	3,354
149	Gum Arabic/	3,036
150	Fiber.mp.	499,870
151	Fibre.mp.	61,625
152	Prebiotic.ti,ab,kw.	10,404
153	Resistant starch.ti,ab,kw.	3,009
154	arabinoxylan.ti,ab,kw.	1,563
155	Beta glucan.ti,ab,kw.	6,523
156	cellulose.ti,ab,kw.	86,776
157	dextrin.ti,ab,kw.	2,386
158	Guar gum.ti,ab,kw.	2,883
159	hemicellulose.ti,ab,kw.	6,363
160	inulin.ti,ab,kw.	13,358
161	pectin.ti,ab,kw.	12,317
162	galactomannan.ti,ab,kw.	4,210
163	fructose oligosaccharide.ti,ab,kw.	10
164	Fructooligosaccharide.ti,ab,kw.	625
165	FOS.ti,ab,kw.	39,750
166	galactose oligosaccharide.ti,ab,kw.	2
167	galactooligosaccharide.ti,ab,kw.	261
168	GOS.ti,ab,kw.	6,939
169	lignin.ti,ab,kw.	20,891
170	methylcellulose.ti,ab,kw.	9,093
171	Alginic acid.ti,ab,kw.	890
172	alginate.ti,ab,kw.	31,140
173	ispagula.ti,ab,kw.	8
174	ispaghula.ti,ab,kw.	227
175	Psyllium.ti,ab,kw.	1,312
176	Acacia gum.ti,ab,kw.	242
177	Gum Arabic.ti,ab,kw.	1,808
178	Artificial feeding/	3,277
179	Enteric feeding/	41,731

180	Nose feeding/	4,627
181	Digestive tract intubation/	4,499
182	Duodenum intubation/	487
183	Stomach intubation/	1,805
184	Dietary supplement/	24,558
185	Nutrition supplement/	6,620
186	Enteral nutrition.mp.	19,790
187	Enteral feeding.mp.	9,973
188	Enteric feeding.mp.	41,802
189	Enteral formula.mp.	728
190	Enteral product.mp.	34
191	(nutrition*2 adj3 support).mp.	35,410
192	EN.ti,ab,kw.	114,739
193	EN modular product.ti,ab,kw.	0
194	Dietary supplement.ti,ab,kw.	9,922
195	Nutrition supplement.ti,ab,kw.	383
196	or/1-130	2,433,924
197	or/131-177	798,780
198	or/178-195	233,695
199	196 and 197 and 198	687
200	Clinical trial/ or Randomized controlled trial/ or Randomization/ or Single blind procedure/ or Double blind procedure/ or Crossover procedure/ or Placebo/ or Randomi?ed controlled trial$.tw. or Rct.tw. or Random allocation.tw. or Randomly allocated.tw. or Allocated randomly.tw. or (allocated adj2 random).tw. or Single blind$.tw. or Double blind$.tw. or ((treble or triple) adj blind$).tw. or Placebo$.tw. or Prospective study/	2,855,272
201	Case study/ or Case report.tw. or Abstract report/ or letter/	1,987,705
202	200 not 201	2,788,218
203	199 and 202	201
204	(exp adolescence/ or exp adolescent/ or exp child/ or exp childhood disease/ or exp infant disease/ or (adolescen* or babies or baby or boy? or boyfriend or boyhood or girlfriend or girlhood or child* or girl? or infan* or juvenil* or juvenile* or kid? or minors or minors* or neonat* or neonat* or neo-nata* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school or school child* or school* or schoolchild* or schoolchild* or teen* or toddler? or underage? or under-age? or youth*).ti,ab,kw.) not exp adult/	4,601,691
205	203 not 204	161
206	(exp animal/ or exp invertebrate/ or nonhuman/ or animal experiment/ or animal tissue/ or animal model/ or exp plant/ or fungus/) not (exp human/ or human tissue/)	8,589,070
207	205 not 206	158

b) Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to January 09, 2024>

#	Query	Results from 11 Jan 2024
1	Critical Care/	61,453
2	Critical Illness/	39,846
3	Intensive Care Units/	71,957
4	intubation, intratracheal/	40,081
5	respiration, artificial/	57,535
6	sepsis/	72,677
7	Bacteremia/	28,273
8	Endotoxemia/	4,811
9	Hemorrhagic Septicemia/	241
10	Fungemia/	3,176
11	Candidemia/	1,595
12	shock/	18,583
13	multiple organ failure/	12,155
14	shock, cardiogenic/	11,018
15	shock, hemorrhagic/	12,389
16	shock, surgical/	1,061
17	shock, traumatic/	4,385
18	systemic inflammatory response syndrome/	7,597
19	cytokine release syndrome/	2,284
20	shock, septic/	25,294
21	Respiratory Distress Syndrome/	25,264
22	Acute lung injury/	8,771
23	Transfusion-related acute lung injury/	141
24	Myocardial infarction/	181,165
25	Heart Arrest/	32,851
26	Out-of-Hospital Cardiac Arrest/	7,373
27	Extracorporeal Membrane Oxygenation/	15,766
28	Multiple Trauma/	13,535
29	Brain Injuries/	56,872
30	Brain Hemorrhage, Traumatic/	240
31	Brain Injuries, Diffuse/	62
32	Brain Injuries, Traumatic/	13,680
33	Liver Failure, Acute/	6,226
34	Acute-On-Chronic Liver Failure/	1,437
35	Pancreatitis, Acute Hemorrhagic/	5
36	Pancreatitis, Acute Necrotizing/	3,872
37	Acute Kidney Injury/	55,763
38	Continuous Renal Replacement Therapy/	872
39	Hemofiltration/	4,816
40	Hemodiafiltration/	2,642
41	Hybrid renal replacement therapy/	33
42	Intermittent renal replacement therapy/	33
43	Burns/	49,129
44	Burns, Chemical/	6,767
45	Burns, Electric/	2,492
46	Burn units/	2,994
47	critical care.mp.	91,150
48	intensive care.mp.	236,527
49	critical illness.mp.	46,916
50	critically ill.mp.	62,163
51	ICU.ti,ab,kw.	87,343
52	Mechanical*2 ventilat*3.ti,ab,kw.	71,312
53	intubat*3.ti,kw.	20,153
54	Sepsis.mp.	154,159
55	Septicemia.mp.	16,126
56	Septic shock.mp.	28,400
57	Shock.ti,ab,kw.	208,885
58	Multiple organ failure.ti,ab,kw.	8,481
59	Multiple organ dysfunction syndrome.ti,ab,kw.	2,784

60	MODS.ti,ab,kw.	2,473
61	Systemic inflammatory response syndrome.ti,ab,kw.	6,133
62	Acute respiratory distress syndrome.mp.	23,764
63	ARDS.ti,ab,kw.	19,926
64	Acute lung injury.ti,ab,kw.	17,503
65	Myocardial infarction.ti,ab,kw.	213,853
66	Cardiac arrest.ti,ab,kw.	44,349
67	Extracorporeal Membrane Oxygenation.ti,ab,kw.	17,678
68	ECMO.ti,ab,kw.	13,126
69	Multiple trauma.ti,ab,kw.	3,475
70	Polytrauma.ti,ab,kw.	4,564
71	Multitrauma.ti,ab,kw.	323
72	Brain injur*3.ti,ab,kw.	85,960
73	Traumatic brain injury.ti,ab,kw.	48,183
74	TBI.ti,ab,kw.	32,291
75	Acute Liver failure.ti,ab,kw.	8,245
76	Acute pancreatitis.ti,ab,kw.	28,166
77	Acute kidney injury.ti,ab,kw.	39,623
78	Acute kidney injury.ti,ab,kw.	39,623
79	AKI.ti,ab,kw.	22,295
80	Continuous renal replacement therapy.ti,ab,kw.	3,777
81	CRRT.ti,ab,kw.	2,586
82	Sustained low efficiency dialysis.ti,ab,kw.	178
83	SLED.ti,ab,kw.	1,294
84	Intermittent h?emodialysis.ti,ab,kw.	1,549
85	Burn unit.ti,ab,kw.	1,399
86	Burn patient.ti,ab,kw.	1,153
87	dietary fiber/	19,863
88	prebiotics/	4,378
89	resistant starch/	309
90	Alginates/	15,109
91	Alginic acid/	96
92	beta glucan/	5,134
93	Cellulose/	34,569
94	Methylcellulose/	4,837
95	Lignin/	14,042
96	Dextrin/	1,114
97	Inulin/	7,510
98	Pectin/	7,172
99	Mannans/	6,538
100	Oligosaccharides, Branched-Chain/	134
101	Xylans/	3,742
102	Psyllium/	744
103	Gum Arabic/	998
104	Fiber.mp.	218,188
105	Fibre.mp.	45,548
106	Prebiotic.ti,ab,kw.	9,306
107	Resistant starch.ti,ab,kw.	2,718
108	Alginic acid.ti,ab,kw.	691
109	alginate.ti,ab,kw.	25,714
110	Beta glucan.ti,ab,kw.	5,795
111	cellulose.ti,ab,kw.	75,359
112	dextrin.ti,ab,kw.	1,654
113	Guar gum.ti,ab,kw.	2,120
114	hemicellulose.ti,ab,kw.	6,504
115	inulin.ti,ab,kw.	9,793
116	pectin.ti,ab,kw.	11,372
117	galactomannan.ti,ab,kw.	2,728
118	lignin.ti,ab,kw.	21,529
119	methylcellulose.ti,ab,kw.	6,223
120	fructose oligosaccharide.ti,ab,kw.	5
121	Fructooligosaccharide.ti,ab,kw.	512
122	FOS.ti,ab,kw.	33,130

123	galactose oligosaccharide.ti,ab,kw.	4
124	galactooligosaccharide.ti,ab,kw.	207
125	GOS.ti,ab,kw.	4,668
126	arabinoxylan.ti,ab,kw.	1,513
127	ispagula.ti,ab,kw.	5
128	ispaghula.ti,ab,kw.	152
129	Psyllium.ti,ab,kw.	913
130	Acacia gum.ti,ab,kw.	174
131	Gum Arabic.ti,ab,kw.	1,616
132	Nutritional support/	7,222
133	Enteral nutrition/	22,146
134	Intubation, Gastrointestinal/	10,297
135	Food, formulated/	6,225
136	Dietary Supplements/	76,010
137	Enteral nutrition.mp.	26,633
138	Enteral feeding.mp.	6,373
139	Enteric feeding.mp.	90
140	Enteral formula.mp.	506
141	Enteral product.mp.	22
142	(nutrition*2 adj3 support).mp.	19,595
143	EN.ti,ab,kw.	113,624
144	EN modular product.ti,ab,kw.	0
145	Dietary supplement.ti,ab,kw.	7,584
146	Nutrition supplement.ti,ab,kw.	235
147	or/1-86	1,397,472
148	or/87-131	475,490
149	or/132-146	245,516
150	147 and 148 and 149	322
151	Randomized controlled trials as Topic/ or Randomized controlled trial/ or Random allocation/ or Double blind method/ or Single blind method/ or Clinical trial/ or exp Clinical Trials as Topic/	1,336,810
152	((clinic$ adj trial$1) or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3))).tw. or Placebos/ or Placebo$.tw. or Randomly allocated.tw. or (allocated adj2 random).tw.	805,409
153	151 or 152	1,712,825
154	Case report.tw. or Letter/ or Historical article/ or Review of reported cases.pt. or Review, multi-case.pt.	2,003,756
155	153 not 154	1,673,140
156	150 and 155	96
157	(exp adolescent/ or exp child/ or exp infant/ or (infant disease* or childhood disease*).ti,ab,kf. or (adolescen* or babies or baby or boy? or boyfriend or boyhood or girlfriend or girlhood or child* or girl? or infan* or juvenil* or kid? or minors or minors* or neonat* or neo-nat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler? or underage? or under-age? or youth*).ti,ab,kf. or (pediatric* or paediatric* or infan* or child* or adolescen* or young).jn,jw. or (pediatric* or paediatric* or infan* or child* or adolescen* or young).in.) not exp adult/	3,696,273
158	156 not 157	71
159	(exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or exp plant/ or exp fungus/) not exp human/	5,619,584
160	158 not 159	66

c) EBM Reviews - Cochrane Central Register of Controlled Trials <December 2023>

#	Query	Results from 11 Jan 2024
1	Critical Care/	2,269
2	Critical Illness/	3,254
3	Intensive Care Units/	3,302
4	intubation, intratracheal/	4,459
5	respiration, artificial/	4,297
6	sepsis/	3,423
7	Bacteremia/	962
8	Endotoxemia/	335
9	Hemorrhagic Septicemia/	0
10	Fungemia/	78
11	Candidemia/	49
12	shock/	759
13	multiple organ failure/	629
14	shock, cardiogenic/	413
15	shock, hemorrhagic/	158
16	shock, surgical/	10
17	shock, traumatic/	61
18	systemic inflammatory response syndrome/	541
19	cytokine release syndrome/	114
20	shock, septic/	1,269
21	Respiratory Distress Syndrome/	1,941
22	Acute lung injury/	713
23	Transfusion-related acute lung injury/	8
24	Myocardial infarction/	13,057
25	Heart Arrest/	1,581
26	Out-of-Hospital Cardiac Arrest/	719
27	Extracorporeal Membrane Oxygenation/	300
28	Multiple Trauma/	292
29	Brain Injuries/	2,301
30	Brain Hemorrhage, Traumatic/	7
31	Brain Injuries, Diffuse/	3
32	Brain Injuries, Traumatic/	1,020
33	Liver Failure, Acute/	103
34	Acute-On-Chronic Liver Failure/	129
35	Pancreatitis, Acute Hemorrhagic/	0
36	Pancreatitis, Acute Necrotizing/	168
37	Acute Kidney Injury/	2,006
38	Continuous Renal Replacement Therapy/	95
39	Hemofiltration/	441
40	Hemodiafiltration/	356
41	Hybrid renal replacement therapy/	0
42	Intermittent renal replacement therapy/	0
43	Burns/	1,775
44	Burns, Chemical/	46
45	Burns, Electric/	15
46	Burn units/	49
47	critical care.mp.	5,044
48	intensive care.mp.	30,611
49	critical illness.mp.	4,572
50	critically ill.mp.	8,729
51	ICU.ti,ab,kw.	17,802
52	Mechanical*2 ventilat*3.ti,ab,kw.	15,121
53	intubat*3.ti,kw.	11,227
54	Sepsis.mp.	13,430
55	Septicemia.mp.	713
56	Septic shock.mp.	3,745
57	Shock.ti,ab,kw.	12,562
58	Multiple organ failure.ti,ab,kw.	1,077
59	Multiple organ dysfunction syndrome.ti,ab,kw.	278

60	MODS.ti,ab,kw.	333
61	Systemic inflammatory response syndrome.ti,ab,kw.	916
62	Acute respiratory distress syndrome.mp.	2,397
63	ARDS.ti,ab,kw.	2,676
64	Acute lung injury.ti,ab,kw.	1,058
65	Myocardial infarction.ti,ab,kw.	32,885
66	Cardiac arrest.ti,ab,kw.	4,456
67	Extracorporeal Membrane Oxygenation.ti,ab,kw.	735
68	ECMO.ti,ab,kw.	932
69	Multiple trauma.ti,ab,kw.	432
70	Polytrauma.ti,ab,kw.	191
71	Multitrauma.ti,ab,kw.	19
72	Brain injur*3.ti,ab,kw.	7,379
73	Traumatic brain injury.ti,ab,kw.	4,422
74	TBI.ti,ab,kw.	3,084
75	Acute Liver failure.ti,ab,kw.	254
76	Acute pancreatitis.ti,ab,kw.	2,183
77	Acute kidney injury.ti,ab,kw.	3,908
78	Acute kidney injury.ti,ab,kw.	3,908
79	AKI.ti,ab,kw.	2,338
80	Continuous renal replacement therapy.ti,ab,kw.	529
81	CRRT.ti,ab,kw.	480
82	Sustained low efficiency dialysis.ti,ab,kw.	35
83	SLED.ti,ab,kw.	124
84	Intermittent h?emodialysis.ti,ab,kw.	177
85	Burn unit.ti,ab,kw.	123
86	Burn patient.ti,ab,kw.	279
87	dietary fiber/	2,130
88	prebiotics/	409
89	resistant starch/	32
90	Alginates/	295
91	Alginic acid/	40
92	beta glucan/	194
93	Cellulose/	481
94	Methylcellulose/	141
95	Lignin/	12
96	Dextrin/	42
97	Inulin/	290
98	Pectin/	19
99	Mannans/	286
100	Oligosaccharides, Branched-Chain/	0
101	Xylans/	43
102	Psyllium/	210
103	Gum Arabic/	35
104	Fiber.mp.	11,226
105	Fibre.mp.	3,228
106	Prebiotic.ti,ab,kw.	1,427
107	Resistant starch.ti,ab,kw.	472
108	Alginic acid.ti,ab,kw.	67
109	alginate.ti,ab,kw.	878
110	Beta glucan.ti,ab,kw.	488
111	cellulose.ti,ab,kw.	1,942
112	dextrin.ti,ab,kw.	292
113	Guar gum.ti,ab,kw.	282
114	hemicellulose.ti,ab,kw.	32
115	inulin.ti,ab,kw.	1,216
116	pectin.ti,ab,kw.	349
117	galactomannan.ti,ab,kw.	103
118	lignin.ti,ab,kw.	43
119	methylcellulose.ti,ab,kw.	310
120	fructose oligosaccharide.ti,ab,kw.	54
121	Fructooligosaccharide.ti,ab,kw.	131
122	FOS.ti,ab,kw.	489

123	galactose oligosaccharide.ti,ab,kw.	26
124	galactooligosaccharide.ti,ab,kw.	62
125	GOS.ti,ab,kw.	884
126	arabinoxylan.ti,ab,kw.	96
127	ispagula.ti,ab,kw.	18
128	ispaghula.ti,ab,kw.	72
129	Psyllium.ti,ab,kw.	395
130	Acacia gum.ti,ab,kw.	24
131	Gum Arabic.ti,ab,kw.	57
132	Nutritional support/	494
133	Enteral nutrition/	2,136
134	Intubation, Gastrointestinal/	743
135	Food, formulated/	815
136	Dietary Supplements/	14,102
137	Enteral nutrition.mp.	5,080
138	Enteral feeding.mp.	1,690
139	Enteric feeding.mp.	1,852
140	Enteral formula.mp.	255
141	Enteral product.mp.	11
142	(nutrition*2 adj3 support).mp.	3,155
143	EN.ti,ab,kw.	8,445
144	EN modular product.ti,ab,kw.	0
145	Dietary supplement.ti,ab,kw.	3,777
146	Nutrition supplement.ti,ab,kw.	232
147	or/1-86	133,355
148	or/87-131	21,064
149	or/132-146	34,115
150	147 and 148 and 149	139

2. Critical Care Nutrition (CCN) methodological quality scoring system

	Score		
	0	**1**	**2**
Randomization		Not concealed or not sure ☐	Concealment of allocation* ☐
Analysis	Other ☐		Intention to treat ☐
Blinding	Not blinded ☐	Single blinded *Check who was blinded:* Health Care Professionals ☐ Outcomes Assessors ☐	Double blinded ☐
Patient selection	Selected patients or unable to tell ☐	Consecutive eligible patients ☐	
Comparability of groups at baseline	No or not sure ☐	Yes ☐	
Extent of follow-up	< 100% ☐	100% ☐	
Treatment protocol	Poorly described ☐	Reproducibly described ☐	
Co-interventions**	Not described ☐	Described but not equal or not sure ☐	Well described and all equal ☐
Outcomes	Not described ☐	Partially described ☐	Objectively defined ☐

* Concealment of allocation means the person enrolling the patients is unaware of the next treatment assignment (e.g. phone in randomization, computer generated).

** Extent to which antibiotics, ventilation, oxygen, transfusions, etc were applied equally across groups

3. Trial Sequential Analysis

Type I and type II errors can influence a SRMA, resulting in incorrect conclusions and inappropriate clinical practices. In conventional meta-analyses, the practice of maintaining a universal statistical threshold at $p < 0.05$ regardless of the total sample size and number of multiple testing can lead to false-positive results. To minimize type I error, a TSA imposes a high threshold for statistical significance (p-value much smaller than 0.05) in earlier trials and becomes less restrictive as the sample size increases with each additional trial. To achieve this, TSA boundaries are constructed. Crossing these boundaries indicates a high certainty of the presence of either a positive or negative effect. Futility boundaries are also constructed to control type II error. Crossing the futility boundaries indicates evidence of an absence of effect, suggesting that continuing to collect data might be futile in terms of finding a significant effect. Not crossing both the futility and TSA boundaries implies that the evidence is inconclusive and that more trials are needed to confirm the presence or absence of an effect [1].

We performed TSA with the following parameters: alpha 5%, beta 10%, and the DerSimonian-Laird random-effect model with a constant continuity correction of 0.5 per group for zero-event studies. Between-trial heterogeneity was adjusted by the diversity-estimate (D^2). For overall mortality and diarrhea incidence, event rates in the control group were estimated from the pooled observed event rate in the current meta-analysis. For ICU and hospital LOS the variance was based on the pooled observed standard deviation in the current meta-analysis. We pre-specified the relative risk reduction (RRR) for overall mortality (10%) and diarrhea incidence (25%), and the minimally relevant difference (MIREDIF) for ICU and hospital LOS (both 1 day) on a clinically meaningful magnitude. Post-hoc, we performed sensitivity analyses for a RRR of 20% and 30% for mortality and 15% and 35% for diarrhea incidence. Additionally, we conducted sensitivity analyses for a MIREDIF of 2 and 3 days for ICU and hospital LOS.

3. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5-6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Suppl. file, Part 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6-7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6-7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 6-7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the	Page 7-8

Section and Topic	Item #	Checklist item	Location where item is reported
		model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 7-8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 9-10
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 9; Suppl. file, Table S9
Study characteristics	17	Cite each included study and present its characteristics.	Page 11; Suppl. file, Table S1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 10; Suppl. file, Table S9 and Fig. S1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Fig. 2 – 5; Suppl. file, Fig. S2-S8, Table S11
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Fig. S1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 11-19; Fig. 2 – 5; Suppl. file, Fig. S2-S8, Table S11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 11-13
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	15-16
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 11-15; Fig.

Section and Topic	Item #	Checklist item	Location where item is reported
			S9-S16
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 18-19; Table 2
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 19
	23b	Discuss any limitations of the evidence included in the review.	Page 21
	23c	Discuss any limitations of the review processes used.	Page 21
	23d	Discuss implications of the results for practice, policy, and future research.	Page 20-21
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 3
Competing interests	26	Declare any competing interests of review authors.	Page 3
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 3

PART 2: Details of the characteristics, intervention, outcomes, and quality scoring of the included studies, and the list of excluded studies

Table S1: Characteristics of included studies and patients

Reference No	Author, year (country)	Single- or Multicenter; N	n; Patient Population	Age		Sex (Male/Female)		Disease severity		MV n (%)		Admission category n (%)		Weight, kg or BMI, kg/m²	
				Fiber	Control	Fiber	Control	Fiber	Control	Fiber	Control	Fiber	Control	Fiber	Control
[38]	Hart, 1988 (Australia)	Single-center	68 (90 randomized); ICU, starting on enteral tube feeds	47.1 ± 20.8	48.5 ± 18.6	22/13	21/12	NR	NR	NR	NR	NR	NR	NR	NR
[39]	Dobb, 1990 (Australia)	Single-center	91 (137 randomized); adult patients in the ICU	47 ± 19	45 ± 19	29/16	32/14	NR	NR	NR	NR	NR	NR	NR	NR
[47]	Celaya, 1992 (Spain)	Single-center	35; ICU, with trauma or sepsis and stress diabetes, expected EN ≥ 14d	48 ± 15	43 ± 12	5/12	7/11	APACHE II: 23.8 ± 5.6	APACHE II: 21.5 ± 4.7	9/17 (52.9)	8/18 (44.4)	NR	NR	NR	NR
[35]	Caparrós, 2000 (Spain)	Multicenter; 15	220 (237 randomized); age ≥ 18, ICU, APACHE II ≥ 8, MOD ≤ 5, expected EN ≥ 7d	51 (34-69)	58 (37-69)	91/31	92/30	APACHE II: 17 (13-20)	APACHE II: 16 (13-21)	118/122 (96.7)	96/98 (98)	Medical 63/122 (52) Surgical 11/122 (9) Trauma 48/122 (39)	Medical 50/98 (51) Surgical 12/98 (12) Trauma 36/98 (37)	NR	NR
[41]	Schultz, 2000 (USA)	Single-center	44 (80 randomized); age ≥ 18, ICU, antibiotics administration, need of EN	fiber + placebo 62.6 ± 14.9 fiber-free + pectin 72.8 ± 13.1 fiber + pectin 60.4 ± 16.1 pooled: 65.27 ± 14.98	66.5 ± 19.2	17/16 [fiber + placebo 6/5 fiber-free + pectin 5/6 fiber + pectin 6/5]	7/4	APACHE II: fiber + placebo 17.3 ± 6.12 fiber-free + pectin 17.8 ± 4 fiber + pectin 15.4 ± 5.8 pooled: 16.83 ± 5.47 Acuity score: fiber + placebo 5.6 ± 0.52 fiber-free + pectin 5.5 ± 0.97 fiber + pectin 5.5 ± 0.69 pooled: 5.53 ± 0.76	APACHE II: 17.9 ± 6.33 Acuity score: 5.4 ± 0.52	NR	NR	Surgical 5/33 (15.2) Medical 16/33 (48.5) Trauma 4/33 (12.1) Neurological 7/33 (21.2)	Surgical 4/11 (36.4) Medical 2/11 (18.2) Trauma 2/11 (18.2) Neurological 2/11 (18.2) Other 1/11 (9.09)	NR	NR

Reference No	Author, year (country)	Single- or Multicenter; N	n; Patient Population	Age		Sex (Male/Female)		Disease severity		MV n (%)		Admission category n (%)		Weight, kg or BMI, kg/m²	
				Fiber	Control	Fiber	Control	Fiber	Control	Fiber	Control	Fiber	Control	Fiber	Control
[43]	Spapen, 2001 (Belgium)	Single-center	25 (35 randomized); adult medical ICU, severe sepsis or septic shock	68 ± 11	69 ± 15	7/6	6/6	APACHE II: 26 ± 7	APACHE II: 24 ± 8	13/13 (100)	12/12 (100)	100% medical	100% medical	NR	NR
[40]	Rushdi, 2004 (Egypt)	Single-center	20 (30 randomized); ICU, age ≥ 20, on EN with ≥ 3 liquid stools/day, APACHE II 16-22	53 ± 14	62 ± 12	6/4	5/5	APACHE II: 18 ± 2 Sickness score: 7 ± 2	APACHE II: 18 ± 2 Sickness score: 7 ± 2	NR	NR	NR	NR	70 ± 13 kg25.1 ± 3.1 kg/m²	74 ± 11 kg 26 ± 2.5 kg/m²
[37]	Palmese, 2006 (Italy)	Single-center	84; 18-65 years, ICU, MV, with central venous catheter and foley catheter in the bladder, antibiotics administration, expected survival > 48h (APACHE < 20)	51 ± 13	50 ± 12	23/19	21/21	APACHE II: 17.2 ± 5	APACHE II: 16.9 ± 4	42/42 (100)	42/42 (100)	Medical 29/42 (69) Surgical 9/42 (21.4) Trauma 3/42 (7.14) Intoxication 1/42 (2.38)	Medical 30/42 (71.4) Surgical 10/42 (23.8) Trauma 2/42 (4.76)	NR	NR
[49]	Karakan, 2007 (Turkey)	Single-center	30; with severe acute pancreatitis	47.3 ± 16.8	44.9 ± 11.2	6/9	8/7	APACHE II: 9.4 ± 3.7 Balthazar CT score: 8.5 ± 4.6	APACHE II: 9.6 ± 3.8 Balthazar CT score: 9.1 ± 5.2	NR	NR	NR	NR	24.7 ± 7.8 kg/m²	27.1 ± 9.5 kg/m²
[46]	Spindler-Vesel, 2007 (Slovenia)	Single-center	113 (132 randomized); surgical ICU, multiple injured patients with Injury Severity Score (ISS) > 18, ICU stay ≥ 4 days	36 (22-51)	group 1: 31 (23-50) group 2: 41 (26-54)	NR	NR	APACHE II: 11 (4.5 - 18)	APACHE II: group 1: 14 (11-18) group 2: 8 (4-15)	NR	NR	100% surgical	100% surgical	NR	NR
[45]	Chittawatanarat, 2010 (Thailand)	Single-center	34; surgical ICU; septic patients with broad spectrum antibiotics and total EN	49.2 ± 20.5	51.9 ± 17.4	6/11	6/11	APACHE II: 19.8 ± 4.2 SAP II: 39.9 ± 8.5	APACHE II: 20.2 ± 6.6 SAP II: 40.1 ± 8.6	NR	NR	100% surgical	100% surgical	55.1 ± 9.5 kg	56.9 ± 15.3 kg
[52]	Zavertailo, 2010 (Russia)	Single-center	56; 18-60 years, ICU, traumatic brain injury and haemorrhagic stroke, MV, expected MV duration ≥ 5 days	45.4 ± 10.7	40.2 ± 12.2	25/3	21/7	APACHE II: 7.5 (14-21) GCS: 7 (7-9)	APACHE II: 19 (11-20) GCS: 0 (7-13)	28/28 (100)	28/28 (100)	NR	NR	NR	NR
[53]	Aytünür, 2012 (Turkey)	Single-center	60; ICU, MV, expected MV ≥ 10d	44.63 ± 20.52	46.13 ± 28.50	9/21	16/14	APACHE II: 19 (19-21)	APACHE II: 20 (17-26)	30/30 (100)	30/30 (100)	NR	NR	62.23 ± 4 kg 23.43 ± 2.43 kg/m²	65.17 ± 14.9 kg 22.73 ± 5.53 kg/m²
[51]	Wang, 2014 (China)	Single-center	86; critically ill trauma patients	40.12 ± 8.13	41.57 ± 8.76	30/13	28/15	NR	NR	NR	NR	NR	NR	NR	NR

Reference No	Author, year (country)	Single- or Multicenter; N	n; Patient Population	Age		Sex (Male/Female)		Disease severity		MV n (%)		Admission category n (%)		Weight, kg or BMI, kg/m²	
				Fiber	Control	Fiber	Control	Fiber	Control	Fiber	Control	Fiber	Control	Fiber	Control
[36]	Kamarul Zaman, 2016 (Malaysia)	Single-center	88; age ≥ 18, critically ill patients, ICU, expected EN ≥ 5 days	56 (33)	54.5 (28)	21/14	23/10	SOFA: 8 ± 6.5 SAPS2: 37.8 ± 16.4	SOFA: 9 ± 4.5 SAPS2: 45.3 ± 16.2	NR	NR	NR	NR	23.9 (10.8) kg/m²	24.3 (10.39) kg/m²
[44]	Yagmurdur, 2016 (Turkey)	Single-center	120; 35-90 years, adult medical ICU, with acute cerebrovascular disease, MV, EN	71 ± 14	70 ± 15	24/36	26/34	APACHE II: 15.7 ± 2.9	APACHE II: 15.7 ± 2.6	60/60 (100)	60/60 (100)	100% medical	100% medical	76 ± 10.6 kg 27 ± 4.5 kg/m²	76.7 ± 9.8 kg 27.2 ± 3.7 kg/m²
[54]	Xi, 2017 (China)	Single-center	125 (166 randomized); age ≥ 18, ICU	48.2 ± 13.7	48.7 ± 10.7	35/28	36/26	APACHE II: 12 ± 2.36 SOFA: 8.5 ± 2.8	APACHE II: 12.3 ± 2.75 8.4 ± 3.0	53/63 (84.1)	50/62 (80.7)	NR	NR	22 ± 2.28 kg/m²	22.1 ± 1.58 kg/m²
[50]	Fazilaty, 2018 (Iran)	Single-center	40 (68 randomized); age ≥ 18, MV, ≥ 2 organ-system traumas	43 (29-53)	32 (25.5-43)	18/2	18/2	APACHE III: 62 (56.25-67) GCS: 7 (5-7)	APACHE III: 62 (53.25-64.75) GCS 6 (5-7)	20/20 (100)	20/20 (100)	NR	NR	NR	NR
[42]	Freedberg, 2020 (USA)	Single-center	20 (22 randomized); age ≥ 18, medical ICU, with sepsis, received a broad-spectrum IV antibiotics within the previous 24h, expected EN duration ≥ 3d	< 50 years: 4/10 (40) 50-70 years 4/10 (40) > 70 years 2/10 (20)	< 50 years: 3/10 (30) 50-70 years 3/10 (30) > 70 years 4/10 (40)	5/5	7/3	SOFA: ≤ 6 points: 2/10 (20) 7-10 points: 5/10 (50) ≥ 11 points: 3/10 (30) GCS: 15 points 3/10 (30) 10-14 points 3/10 (30) < 10 points 4/10 (40)	SOFA: ≤ 6 points: 5/10 (50) 7-10 points: 3/10 (30) ≥ 11 points: 2/10 (20) GCS: 15 points 5/10 (50) 10-14 points 4/10 (40) < 10 points 1/10 (10)	NR	NR	100% medical	100% medical	NR	NR
[48]	Chen, 2021 (China)	Single-center	46 (49 randomized); age 18-70, ICU, with severe acute pancreatitis	45 ± 9.07	51.1 ± 12	11/11	11/13	APACHE II: 18.5 ± 7.71 Balthazar CT Score: 6 (4.5-8) Modified Marshall score: 3 (2-3) SOFA: 4.5 (4-6.75)	APACHE II: 18.6 ± 5.65 Balthazar CT Score: 6 (5.75-8) Modified Marshall score: 3 (2-5) SOFA: 6 (4-8)	NR	NR	NR	NR	70 (63.8-80) kg	70 (65-80) kg

APACHE II: acute physiology and chronic health evaluation II, BMI: body mass index, ICU: intensive care unit, Med: medical, MV: mechanical ventilation, N: number of center, n: sample size, SAPS II: simplified acute physiology score II, GCS: Glasgow Coma Scale, SOFA: sequential organ failure assessment

Table S2: Funding source

Refe-rence No	Author, year	industry/Non-industry/Unclear/None	Grant/Company name	additional information
[38]	Hart, 1988	Industry	Reckitt & Coleman Australia	supplied Fybogel and placebo
[39]	Dobb, 1990	Unclear		
[47]	Celaya, 1992	Unclear		
[35]	Caparrós, 2000	Industry	Nutricia Spain, S.A	
[41]	Schultz, 2000	Industry	1. Sigma Theta Tau International 2. Glaxo-Wellcome	
[43]	Spapen, 2001	Industry	Novartis Nutrition, the Netherlands	provided enteral feeds
[40]	Rushdi, 2004	Industry	Novartis Nutrition GmbH, München, Germany	
[37]	Palmese, 2006	Unclear		
[49]	Karakan, 2007	Unclear		
[46]	Spindler-Vesel, 2007	Non-industry	Ministry of Science of Republic of Slovenia	
[45]	Chittawatanarat, 2010	Industry	Nestlé Ltd.	donated both enteral diet formulas free of charge, no financial support
[52]	Zavertailo, 2010	Unclear		
[53]	Aytünür, 2012	Unclear		
[51]	Wang, 2014	Unclear		
[36]	Kamarul Zaman, 2016	Non-industry	University of Malaya	
[44]	Yagmurdur, 2016	Unclear		
[54]	Xi, 2017	Non-industry	1. National Natural Science Foundation of China 2. Jiangsu Province Special Program of Medical Science 3. Jiangsu Province's Key Medical Talent Program 4. Scientific Research Foundation of Graduate School of Nan-jing University	
[50]	Fazilaty, 2018	Non-industry	National Nutrition and Food Technology Research Institute	
[42]	Freedberg, 2020	Non-industry	Feldstein Medical Foundation and Columbia University's Irving Institute	
[48]	Chen, 2021	Unclear		

Table S3: Feeding information

Reference No	Author, year	EN formula in intervention group				EN formula in control group		dosage and frequency of EN	Route of administration	Timing of start of EN/intervention	Duration of EN/intervention
		Brand and company	description	Type and content of fiber(s)	co-intervention (if any)	Brand and company	description				
[38]	Hart, 1988	Osmolite (Abbott Laboratories, North Chicago, USA); "Fybogel" (Reckitt & Colman)	standard formula + fiber	Plantago ovata (Ispaghula husk): 7g/d	No	Osmolite (Abbott Laboratories, North Chicago, USA); "Weetbix" (Sanitarium, Australia)	standard formula + placebo (wheat-based breakfast cereal)	1. day: 40ml/h of half-strength feed 2. day: 40ml/h of full-strength feed ≥ 3. day: increased by 20-40ml/h/d depending on clinical assessment, to a maximum of 120ml/h or more	naso-gastric tube	NR	≥ 3 days
[39]	Dobb, 1990	Enrich (Abbott Australia Pty Ltd.)	iso-osmolar, lactose-free, fiber-enriched	soy polysaccharide: 21g/l	No	Ensure (Abbott Australia Ptd Ltd.)	standard formula, iso-osmolar, lactose-free (fiber-free)	1. day: 40ml/h of half-strength feed 2. day: 40ml/h of full-strength feed ≥ 3. day: increased by 20-40ml/h/day depending on clinical assessment, to a maximum of 120ml/h	naso-gastric tube	NR	≥ 3 days until max. 18 days or discharge from ICU
[47]	Celaya, 1992	Glucerna (Abbott Laboratories)	diet specific for glucose intolerance	soy polysaccharides: 14.4g/1000cal	No	NR	hyperproteic diet without fiber	NR	fine caliber tube (not specified)	NR	≤ 14 days
[35]	Caparrós, 2000	Stresson Multifibre (Nutricia Spain S.A., Madrid, Spain)	high-protein formula with fiber, arginine, medium-chain triglycerides, antioxidants	soy polysacharides: 4.2g/1500ml cellulose: 1.65g/1500ml resistant starch: 1.2g/1500ml inuline: 1.65g/1500ml oligofructose: 1.5g/1500ml arabic gum: 3.3g/1500ml	arginine: 11.8%; 10.05g/1500ml medium-chain triglycerides: 40%; 25.8g/1500ml Vitamin A: 1995µg/1500ml Vitamin C: 200mg/1500ml Vitamin E: 73.8mg/1500ml	Nutrison Protein Plus (Nutricia Spain S.A., Madrid, Spain)	high-protein standard diet (fiber-free)	24h at a constant rate by infusion pump; 42ml/h the first day; increase of volume of 20ml/h every 12 hours until caloric goal (25kcal/kg/day) was achieved	Enteral-gastric or enteral-jejunal tube	within 48 hours of admission	10 (6-18) days
[41]	Schultz, 2000	fiber-enriched: Jevity Plus (NR) pectin: NR	fiber-enriched formula + placebo fiber-free formula + pectin fiber-enriched formula + pectin	fiber-enriched formula: 25% soluble fiber (not specified) pectin (100% soluble fiber): 1.07g/d mean daily fiber in fiber/placebo group: 17.3g mean daily fiber in	No	Osmolite (Abbott, Illinois, USA) or Promote (Abbott Nutrition, Chicago, USA)	standard fiber-free formula + placebo	NR	feeding tube (not specified)	5.8 ± 4.4; 4.6 ± 1.7; 4.7 ± 2.2 days	6 days

Reference No	Author, year	EN formula in intervention group				EN formula in control group		dosage and frequency of EN	Route of administration	Timing of start of EN/intervention	Duration of EN/intervention
		Brand and company	description	Type and content of fiber(s)	co-intervention (if any)	Brand and company	description				
				fiber/pectin group: 15.8g							
[43]	Spapen, 2001	Benefiber (Novartis Nutrition, the Netherlands)	isocaloric, isonitrogenous EN with fiber	partially hydrolyzed guar gum: 22g/l	No	NR	standard isocaloric, isonitrogenous control formula without fiber	25ml/h for the first 24h, then increased by 25-35ml/h until at least 80% of individual energy needs were reached	nasogastric tube	within 24h after randomization	11 ± 4 (≥ 6 days, max. 21 days or withdrawal of EN)
[40]	Rushdi, 2004	Sandosource GI Control (Novartis Nutrition GmbH, München, Germany) + Benefiber (NR)	fiber-enriched feed	soluble guar gum: 2%, 22g/l (22-24g/day)	No	Propeptide (Prime, Nutrition Medical, Inc. USA)	standard fiber-free feed	energy administration (25-23kcal/kg/day) during 18-24h per 24h at a constant rate through pump-assisted system; 50% of required energy intake on first day, 75% on second day, 100% on third + fourth day	nasojejunal tube	NR	4 days
[37]	Palmese, 2006	Jevity (Abbott, Zwolle, The Netherlands)	isocaloric, isonitrogenous EN with fiber	Soluble and insoluble dietary fiber: 10.6g/l (fructooligosaccharides: 7g/l)	i.v. glutamine (both groups): 10g/day	NR	isocaloric, isonitrogenous EN without fiber + i.v. glutamine administration	all patients: bolus of 50ml of EN, both EN and PN were administered to reach target caloric intake (25-23kcal/kg/day) intervention: 2x for 7x hours/day with 5 hours break, overall 1000ml/day	nasogastric tube	within 24h of admission	duration of ICU stay
[49]	Karakan, 2007	NR	calorie-, lipid- and protein-identical to control formula + multifibers	soluble fibers (not specified): 0.7g/100ml insoluble fibers (not specified): 0.8/100ml total: 1.5g/100ml, 24g/d	No	NR	standard calorie-, lipid- and protein-identical without fiber	30ml/h at full strength, increasing to 100ml/h over 24-48h, caloric goal 2000kcal/d all patients received adjuvant peripheral parenteral nutrition with standard solution	nasojejunal tube	within 24h of admission	8 ± 4 (6-12)
[46]	Spindler-Vesel, 2007	Nova Source (Novartis Medical Nutrition, Basel, Switzerland)	EN with fiber	fermentable guar gum: 22g/l	No	group A: Alitraq (Abbott-Ross, Abott Park, IL, USA) group C: Nutricomp peptide (B. Braun, Melsungen, Germany)	group A: EN with glutamine, arginine, linolenic acid group C: peptide diet	30ml/h for 4 hours, interruption for 2 hours to assess gastric intolerance, if volume < 200ml the rate was increased by 50-100%, maximum volume 160ml/h, EN was stopped during 6 night hours, target value: 0.2-0.3 gN/kg/d and 25 nonprotein kcal/kg/day at 72h of admission	intragastric tube	within 24h after injury; intervention: 12.5 (9.6-15); control group A: 15.5 (13-20.3); control group C: 12.8 (10-18)	NR
[45]	Chittawatanarat, 2010	Nutren Fibre (Nestlé Suisse S.A., Switzerland)	mixed fiber formula	overall dietary fiber, produced by yellow pea fiber + fructo-oligosaccharide: 15.1 g/l; soluble:insoluble fiber 1:1;	No	Nutren Optimum (Nestlé Suisse S.A., Switzerland)	standard formula (fiber-free)	NR	feeding tube (not specified)	NR	all patients ≥ 5 days, 8/17 vs. 10/17 14 days (≥ 5 days until max. 14 days

Reference No	Author, year	EN formula in intervention group				EN formula in control group		dosage and frequency of EN	Route of administration	Timing of start of EN/intervention	Duration of EN/intervention
		Brand and company	description	Type and content of fiber(s)	co-intervention (if any)	Brand and company	description				
				soluble fiber: 35% fructo-oligosaccharide, 15% pectin; insoluble fiber: 30% cellulose, 5% lignin, 15% hemicellulose							or change to normal oral diet)
[52]	Zavertailo, 2010	Nutricomp Intensive (Braun, Germany) + Nutricomp ADN Braun Fiber (Braun, Germany)	fluid-restricted formula + fiber-formula	NR	Erythromycin: 300mg first 3 days	NR	standard formula (isocaloric, no fiber), no erythromycin	4x/day with 1h breaks, total feeding duration 18-20h/day; first day: 50ml/h, increase of rate each subsequent day by 25ml/h, maximum rate 125ml/h	nasogastric tube	NR	NR
[53]	Aytünür, 2012	Jevity (Abbott, Zwolle, The Netherlands)	standard fiber iso-osmolar formula	Soluble and insoluble dietary fiber: 10.6g/l (fructooligosaccharides: 7g/l)	No	Osmolite (Abbott, Illinois, USA)	standard iso-osmolar formula (fiber-free)	initial 30ml/h; increase by 20ml/h every 8 hours in patients without complications; no enteral feeding between 24:00 and 08:00	nasogastric tube	NR	3 days
[51]	Wang, 2014	fiber: (Haiyishengyuan Biological Engineering Co., Ltd.)	standard EN + fiber + glutamine	soluble dietary fiber (not specified): 3g/1000kcal	glutamine: 0.5g/kg/day	NR	standard EN	daily energy supply was calculated using a formula	nasogastric tube	NR	NR
[36]	Kamarul Zaman, 2016	Ensure FOS (NR)	EN with fiber	fructooligosaccharide: 10g/l; 14.8g/d	No	Osmolite (Abbott, Illinois, USA)	standard EN	volumes of EN were based on each patient's total energy requirement, which was calculated by attending dietitian	nasogastric tube	0 ± 1 vs. 0 ± 1.5 days	14 days
[44]	Yagmurdur, 2016	Nutrison multifibre (500ml, Nutricia Advanced Medical Nutrition, Netherlands)	fiber-enriched solution	soluble fibers: 7g/l, insoluble fibers: 8g/l soy polysaccharides: 35% arabic gum: 24% inulin: 12.5% alpha-cellulose: 12% oligofructose: 10.5% resistant starch: 9% daily fiber dose: 28g/d	No	Nutrison (500ml, Nutricia Advanced Medical Nutrition, Netherlans)	standard fiber-free solution	target value: 25-35kcal/kg/day; EN 18-24h/day at constant rate; first day: 50% of required energy intake, second day: 75%, 3. day: 100%; EN startes at 20ml/h, increased at six-hour intervals to 40ml/h, 80ml/h,100-120ml/h	nasogastric tube	within 48h after admission	NR
[54]	Xi, 2017	Peptisorb (NR)	control formula + pectin	pectin: 6g each time, 24g/day	No	Peptisorb (NR)	standard EN	both groups: 1. day 5% glucose at 25ml/; 2. day EN (31.3g Peptisorb dissolved in 250ml water) at 12.5ml/h; 3.-6. day EN (62.5g Peptisorb dissolved in 250ml) at a rate of 12.5ml/h; from 7. day EN was advanced to the goal energy target (25kcal/kg/day) as	nasojejunal tube	within 36h after admission	≥ 6 days

Reference No	Author, year	EN formula in intervention group				EN formula in control group		dosage and frequency of EN	Route of administration	Timing of start of EN/intervention	Duration of EN/intervention
		Brand and company	description	Type and content of fiber(s)	co-intervention (if any)	Brand and company	description				
								quickly as possible fiber group: additional amount of pectin was administrated once 4 hours ahead of EN from day 2-6 (24g every day)			
[50]	Fazilaty, 2018	ß-glucan: (Arian Salamat Sina Company, Teheran, Iran)	hospital-prepared standard kitchen formula + ß-glucan	oat ß-glucan: 3g/d	No	None (hospital-prepared)	hospital-prepared standard kitchen formula + placebo (3g/d maltodextrin)	NR	feeding tube (not specified)	within 24-48h of admission	≥ 10 days until 21 days or discharge from ICU
[42]	Freedberg, 2020	Promote 1.0 with Fiber (Abbott Nutrition, Chicago, USA)	mixed fiber formula, calorie- and micronutrient-identical to control formula	oat and soy derived dietary fiber (not specified): 14.3g/l median dose: 11g/d	No	Promote 1.0 (Abbott Nutrition, Chicago, USA)	standard formula, calorie- and micronutrient identical	NR	feeding tube (not specified)	NR	≥ 3 days until withdrawal from study or hospital discharge or day 30 or death
[48]	Chen, 2021	polydextrose: (Tailijie Biotech Co, Ltd, Henan, China)	Control formula + polydextrose	polydextrose (soluble dietary fiber): 20g/day	No	NR	Control formula without fiber	1. day (first 24 hours): EN volume 250ml (= 250kcal), speed 30 ml/h 2. day (24-48 hours): EN volume 500-750ml (=500-750 kcal), speed 40-50ml/h 3. day (48-72 hours): EN volume 750-1250ml (=750-1250 kcal), speed 60-80ml/h > 72 hours: EN volume 1250-2250ml (= 1250-2250 kcal = caloric goal), speed 80-120ml/h	nasojejunal tube	NR	NR

Table S4: Clinical outcomes

Reference No	Author, year	Mortality n (%)		Gastrointestinal complications (not including diarrhea)		Length of stays (days, mean ± SD)		Duration of Ventilation (days, mean ± SD)		Infectious complications n (%)	
		Fiber	Control	Fiber	Control	Fiber	Control	Fiber	Control	Fiber	Control
[38]	Hart, 1988	NR	NR	**abdominal distension** 2/35 (5.71) **ileus or gastric stasis** 4/35 11.4)	**abdominal distension** 0/33 **ileus or gastric stasis** 3/33 (9.09)	NR	NR	NR	NR	NR	NR
[39]	Dobb, 1990	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
[47]	Celaya, 1992	**Unspecified** 4/17 (22.2)	**Unspecified** 5/18 (29.4)	**gastric distension** 2/17 (11.8) **constipation** 3/17 (17.6)	NR	NR	NR	NR	NR	NR	NR
[35]	Caparrós, 2000	**ICU** 19/122 (15.6) **In-hospital** 25/122 (20.5) **6-month** 30/122 (24.6) Medical 17/63 (27) Surgical 4/11 (36.4) Trauma 9/48 (18.8)	**ICU** 21/98 (21.4) **In-hospital** 29/98 (29.6) **6-month** 31/98 (31.6) Medical 19/63 (38) Surgical 5/11 (41.7) Trauma 7/48 (19.4)	*incidence density rates: number of episodes per 1000 days of enteral nutrition* **Bronchial aspiration of gastric contents** 0.7 **Increased gastric residual** 100.1 **Vomiting** 8.7 **Constipation** 4.7 **Abdominal distension** 9.3	*incidence density rates: number of episodes per 1000 days of enteral nutrition* **Bronchial aspiration of gastric contents** 0.9 **Increased gastric residual** 53.7 **Vomiting** 11.4 **Constipation** 15.9 **Abdominal distension** 11.4	**ICU** 15 (9.8-25) **Hospital** 29 (16.8-51)	**ICU** 13 (8.8-20.3) **Hospital** 26 (17.8-42)	10 (5-18)	9 (5-14)	*Infection density rates: number of episodes per 1000 days of ICU LOS* **Overall infections** 37.1 **Bacteremia** 6.8 **Catheter-realted sepsis** 0.4 **Surgical infections** 1.9 **Urinary tract infections** 6.8 *Infection density rate: number of episodes per 1000 days of mechanical ventilation* **Nosocomial pneumonia** 32.2	*Infection density rates: number of episodes per 1000 days of ICU LOS* **Overall infections** 35.1 **Bacteremia** 6.7 **Catheter-realted sepsis** 5.5 **Surgical infections** 1.8 **Urinary tract infections** 3.0 *Infection density rate: number of episodes per 1000 days of mechanical ventilation* **Nosocomial pneumonia** 24.7
[41]	Schultz, 2000	NR	NR	NR	NR	**ICU**: **fiber + placebo** 20.7 ± 8.5 **fiber-free + pectin** 17.3 ± 8.2 **fiber + pectin** 22.1 ± 16.4 **Pooled:** 20.03 ± 11.85 **Hospital**: **fiber + placebo** 42.8 ± 32.5	**ICU** 28 ± 14.6 **Hospital** 34 ± 14.7	NR	NR	NR	NR

Reference No	Author, year	Mortality n (%)		Gastrointestinal complications (not including diarrhea)		Length of stays (days, mean ± SD)		Duration of Ventilation (days, mean ± SD)		Infectious complications n (%)	
		Fiber	Control	Fiber	Control	Fiber	Control	Fiber	Control	Fiber	Control
						fiber-free + pectin 24.4 ± 9 **fiber + pectin** 33.8 ± 22.1 **Pooled**: 33.67 ± 23.64					
[43]	Spapen, 2001	**Hospital** 1/13 (7.7)	**Hospital** 4/12 (33.3)	NR	NR	19 (11-51)	17 (10-30)	11 ± 4	12 ± 5	NR	NR
[40]	Rushdi, 2004	NR	NR	**number of liquid stools:** first day 2 ± 0.9 fourth day 1 ± 0.7 **severe nausea** 0/10 **vomiting** 0/10 **flatulence** 2/10 (20) **constipation** 0/10	**number of liquid stools:** first day 1.2 ± 0.7 fourth day 2.1 ± 0.8 **severe nausea** 0/10 **vomiting** 2/10 (20) **flatulence** 4/10 (40) **constipation** 1/10 (10)	NR	NR	NR	NR	NR	NR
[37]	Palmese, 2006	**Unspecified** 6/42 (14.2)	**Unspecified** 8/42 (19.0)	**patients with gastrointestinal complications:** 11/42 (26.2) **Increase in gastric residua**l 5/42 (11.9) **Regurgitation** 2/42 (4.76) **Vomiting** 5/42 (11.9) **Constipation** 1/42 (2.38) **Abdominal distension** 5/42 (11.9)	**patients with gastrointestinal complications:** 15/42 (35.7) **Increase in gastric residual** 6/42 (14.3) **Regurgitation** 3/42 (7.14) **Vomiting** 4/42 (9.52) **Constipation** 1/42 (2.38) **Abdominal distension** 6/42 (14.3)	**ICU** 12 ± 4.6	**ICU** 13 ± 3.4	6 ± 1.7	5 ± 2.5	**Bacteremia** 2/42 (4.76) **Pneumonia** 2/42 (4.76) **urinary tract infection** 6/42 (14.3) **central line infection** 2/42 (4.76) **soft tissue infection** 0/42 **intrathoracic and/or intra-abdominal infection** 1/42 (2.38) > 1 infection: 3/42 (7.1)	**Bacteremia** 4/42 (9.52) **Pneumonia** 6/42 (14.3) **urinary tract infection** 5/42 (11.9) **central line infection** 5/42 (11.9) **soft tissue infection** 0/42 **intrathoracic and/or intra-abdominal infection** 1/42 (2.38) > 1 infection: 6/42 (14.3)
[49]	Karakan, 2007	**Unspecified** 2/15 (13.3)	**Unspecified** 4/15 (26.7)	**bloating and gas symptoms** 3/15	**bloating and gas symptoms** 0/15	**ICU** 6 ± 2 (5-8) **Hospital** 10 ± 4 (8-14)	**ICU** 6 ± 2 (5-7) **Hospital** 15 ± 6.0 (7-26)	NR	NR	**cholangitis** 1/15 (6.67) **sepsis** 1/15 (6.67)	**cholangitis** 0/15 **sepsis** 2/15 (13.3)
[46]	Spindler-Vesel, 2007	**ICU** 2/29 (6.90)	**ICU** 3/58 (5.17) [group A 1/32 (3.13)] [group C 2/26 (7.69)]	NR	NR	16 (10-21)	group A: 14 (8.3-23) group C: 11.5 (6-20)	10 (6-16)	group A: 12 (8-15) group C: 8 (4-15)	**pneumonia** 12/29 (41.4) **urinary tract** 0/29 **vascular** 1/29 (3.45) **wound** 2/29 (6.90) **positive hemocultures** 2/29 (6.90) **others** 0/29	**pneumonia** 22/58 (37.9) [group A 11/32 (34.4), group C 11/26 (42.3)] **urinary tract** 1/58 [group A 1/32 (3.13), group C 0/26] **vascular** 1/58 (1.72)

Reference No	Author, year	Mortality n (%)		Gastrointestinal complications (not including diarrhea)		Length of stays (days, mean ± SD)		Duration of Ventilation (days, mean ± SD)		Infectious complications n (%)	
		Fiber	Control	Fiber	Control	Fiber	Control	Fiber	Control	Fiber	Control
											[group A 1/32 (3.13), group C 0/26] **wound** 3/58 (5.17) [group A 1/32 (3.13), group C 2/26 (7.69) **positive hemocultures** 1/58 (1.72) [group A 1/32 (3.13), group C 0/26] **others** 1/58 [group A 1/32 (3.13, group C 0/26]
[45]	Chitta-watanarat, 2010	**Unspecified** 1/17 (5.88)	**Unspecified** 2/17 (11.8)	NR	NR	**surviving patients:** **ICU** 16.8 ± 8 (6-37) **Hospital** 30.9 ± 28 (6-120)	**surviving patients:** **ICU** 25.5 ± 13 (11-50) **Hospital** 36.1 ± 14.8 (15-61)	NR	NR	NR	NR
[52]	Zavertailo, 2010	**30-day** 3/28 (10.7)	**30-day** 3/28 (10.7)	NR	NR	**ICU** 25.8 ± 14	**ICU** 32.6 ± 25.4	20.3 ± 11	25.8 ± 20.2	NR	NR
[53]	Aytünür, 2012	NR	NR	**Abdominal distension** 1. day 4/30 (13.33) 2. day 7/30 (23.33) 3. day 3/30 (10) **Vomiting** 1. day 0/30 2. day 2/30 (6.66) 3. day 3/30 (10) **Regurgitation** 1. day 1/30 (3.33) 2. day 8/30 (26.6) 3. day 6/30 (20) **Aspiration** 0/30 **≥ 1 complication**: 20/30 (66.66)	**Abdominal distension** 1. day 4/30 (13.33) 2. day 2/30 (6.66) 3. day 3/30 (10) **Vomiting** 1. day 0/30 2. day 2/30 (6.66) 3. day 4/30 (13.33) **Regurgitation** 1. day 0/30 2. day 8/30 (26.6) 3. day 6/30 (20) **Aspiration** 0/30 **≥ 1 complication**: 17/30 (56.66)	NR	NR	NR	NR	NR	NR
[51]	Wang, 2014	NR	NR	**constipation** 6/43 (13.95) **nausea** 0/43 **vomiting** 0/43	**constipation** 13/43 (30.23) **nausea** 0/43 **vomiting** 0/43	NR	NR	NR	NR	NR	NR

Reference No	Author, year	Mortality n (%)		Gastrointestinal complications (not including diarrhea)		Length of stays (days, mean ± SD)		Duration of Ventilation (days, mean ± SD)		Infectious complications n (%)	
		Fiber	Control	Fiber	Control	Fiber	Control	Fiber	Control	Fiber	Control
				digestive bleeding 0/43	**digestive bleeding** 0/43						
[36]	Kamarul Zaman, 2016	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
[44]	Yagmurdur, 2016	NR	NR	**Regurgitation** 10/60 (16.7) **Vomiting** 9/60 (15) **Distension** 25/60 (41.7) **Constipation** 2/60 (3.33)	**Regurgitation** 9/60 (15) **Vomiting** 10/60 (16.7) **Distension** 18/60 (30) **Constipation** 2/60 (3.33)	NR	NR	NR	NR	NR	NR
[54]	Xi, 2017	**30-day** 1/62 (1.61)	**30-day** 3/63 (4.8)	**Gastrointestinal intolerance** 17/62 (27.4) **vomiting** 2/62 (3.2) **abdominal distension or cramping** 4/62 (6.5) **constipation** 2/62 (3.2) **Regurgitation** 3/62 (4.8)	**Gastrointestinal intolerance** 26/63 (41.3) **vomiting** 3/63 (4.8) **abdominal distension or cramping** 5/63 (7.9) **constipation** 7/63 (11.1) **Regurgitation** 5/63 (7.9)	**ICU** 13.8 ± 8.59 **Hospital** 23.4 ± 13.2	**ICU** 17.9 ± 9.72 **Hospital** 32.9 ± 19	NR	NR	7/62 (11.3)	9/63 (14.3)
[50]	Fazilaty, 2018	**Unspecified** 1/20 (5.00)	**Unspecified** 4/20 (20.0)	NR	NR	**ICU** 27.55 ± 7.8	**ICU** 31.2 ± 15.8	15 (10-22.5)	28 (11-39.75)	**infection rate** 5/20 (25) **ventilator associated pneumonia** 4/20 (20.0) **urinary tract** 0/20 **wound** 2/20 (10.0) **sepsis** 0/20 **central nervous system** 0/20	**infection rate** 11/20 (55) **ventilator associated pneumonia** 4/20 (20.0) **urinary tract** 4/20 (20.0) **wound** 4/20 (20.0) **sepsis** 2/20 (10.0) **central nervous system** 3/20 (15.0)
[42]	Freedberg, 2020	**Unspecified** 2/10 (20.0)	**Unspecified** 4/10 (40.0)	NR	NR	NR	NR	NR	NR	**culture-proven infections 3/10 (30.0)**	**culture-proven infections** 3/10 (30.0)
[48]	Chen, 2021	**28-day** 0/24 (0)	**28-day** 1/22 (4.55)	**Feeding intolerance** 6/24 (25) **Abdominal distension** 7/24 (29.2) **Vomiting** 2/24 (8.33) **Constipation** 3/24 (12.5) **Gastrointestinal bleeding** 2/24 (8.33)	**Feeding intolerance** 13/22 (59.1) **Abdominal distension** 16/22 (72.7) **Vomiting** 2/22 (9.09) **Constipation** 16/22 (72.7) **Gastrointestinal bleeding** 1/22 (4.55)	**ICU** 10 (6.25-13.8) **Hospital** 17.5 (15-26)	**ICU** 13 (10.5-16-8) **Hospital** 17.5 (15-26)	NR	NR	**urinary tract infection** 0/24 **intra-abdominal infection** 1/24 (4.17) **systemic infection** 1/24 (4.17) **intravascular catheter-related infection** 2/24 (8.33)	**urinary tract infection** 2/22 (9.09) **intra-abdominal infection** 3/22 (13.6) **systemic infection** 0/22 **intravascular catheter-related infection** 1/22 (4.55)

Table S5: Metabolic and nutritional outcomes

Reference No	Author, year	Metabolic outcomes (Blood glucose, triglyceride)		Nutritional indices	
		Fiber	Control	Fiber	Control
[38]	Hart, 1988	NR	NR	**mean daily feed volumes:** 1537ml **1. day** 688 ± 204 **10. day** 2066 ± 463	**mean daily feed volumes**: 1605ml **1. day** 628 ± 225 **11. day** 2010 ± 536
[39]	Dobb, 1990	NR	NR	**feed volumes** 1. day 380 ± 172ml	**feed volumes** 1. day 494 ± 265ml
[47]	Celaya, 1992	**blood glucose (mg/dl):** overall mean 156.34 ± 24 **serum triglyceride (mg/dl):** 1. day 154 ± 45 7. day 148 ± 36 14. day 137 ± 22	**blood glucose (mg/dl):** overall mean 191.83 ± 46 **serum triglyceride (mg/dl):** 1. day 139 ± 28 7. day 154 ± 39 14. day 176 ± 54	NR	NR
[35]	Caparrós, 2000	NR	NR	**administered caloric intake day 3** (kcal/day): 1625 (1137-1828) **administered caloric intake day 7** (kcal/day): 1538 (1169-1863)	**administered caloric intake day 3** (kcal/day): 1625 (1314-1897) **administered caloric intake day 7** (kcal/day): 1750 (1259-1963)
[41]	Schultz, 2000	NR	NR	NR	NR
[43]	Spapen, 2001	NR	NR	**time to reach preconceived protein/caloric goals:** 5 ± 3 days	**time to reach preconceived protein/caloric goals**: 6 ± 3 days
[40]	Rushdi, 2004	**plasma glucose at end of study (day 5) (mg/dl):** 126 ± 81 (vs. Day 1 333 ± 208) **serum cholesterol (mg/dl) at end of study (day 5):** 164 ± 71 (vs. Day 1 378 ± 26)	NR	**feed volumes 1. day:** 1070 ± 221 ml **feed volumes 4. day:** 1775 ± 450 ml	**feed volumes 4. day:** 1070 ± 604 ml
[37]	Palmese, 2006	NR	NR	NR	NR
[49]	Karakan, 2007	NR	NR	NR	NR
[46]	Spindler-Vesel, 2007	NR	NR	**average GRV first week:** 740 (530-1510) ml **volume of EN first 24h:** 430 (100-600) ml **total volume of EN during first 4 days:** 3250 (2400-3700) ml	**average GRV first week**: group A: 410 (382-1062) ml group C: 620 (337-1190) ml **volume of EN first 24h:** group A: 250 (157-562) ml group C: 387 (87-740) **total volume of EN during first 4 days:** group A: 2720 (2356-3700) ml group C: 2675 (1515-3908) ml
[45]	Chittawatanarat, 2010	NR	NR	**mean caloric delivery of 1500kcal:** achieved at day 6	**mean caloric delivery of 1500kcal:** achieved at day 8
[52]	Zavertailo, 2010	NR	NR	**caloric delivery (kcal/kg/day) on 10. day:** 31.8 ± 10.5 **energy balance (kcal/day) on 10. day:** -404 ± 1007	**caloric delivery (kcal/kg/day) on 10. day:** 20.6 ± 10.1 **energy balance (kcal/day) on 10. day:** -1359 ± 1078

Refe-rence No	Author, year	Metabolic outcomes (Blood glucose, triglyceride)		Nutritional indices	
		Fiber	Control	Fiber	Control
				nitrogen balance (g/day) on 10. day: -5.55 ± 9.61	**nitrogen balance (g/day) on 10. day:** -10.3 ± 7.9
[53]	Aytünür, 2012	NR	NR	**time to reach target calories:** 4 (3-6) days **Gastric residual volume** (ml): 1. day 8:00 32.17 ± 47.61 16:00 57.67 ± 85.92 24:00 58.33 ± 69.04 2. day 8:00 54.33 ± 81.32 16:00 43 ± 97.49 24:00 47.83 ± 116.07 3. day 8:00 56.83 ± 92.80 16:00 60.83 ± 88.7 24:00 85.67 ± 168.84	**time to reach target calories:** 4 (3-6) days **Gastric residual volume** (ml) 1. day 8:00 34.76 ± 44.16 16:00 47.5 ± 53.27 24:00 48 ± 69.74 2. day 8:00 46.33 ± 63.87 16:00 48.83 ± 69.74 24:00 45 ± 72.08 3. day 8:00 35.33 ± 67.09 16:00 44.33 ± 64.82 24:00 30.5 ± 49.49
[51]	Wang, 2014	NR	NR	NR	NR
[36]	Kamarul Zaman, 2016	NR	NR	**nutritional intake (kcal/day):** 1465.2 ± 337.4	**nutritional intake (kcal/day):** 1501.7 ± 396.7
[44]	Yagmurdur, 2016	NR	NR	**daily GRV**: 1. day 113 ± 96 2. day 128 ± 116 3. day 126 ± 98 4. day 129 ± 100 5. day 122 ± 93 **mean daily volume ratio (%):** 84.2 ± 9.8	**daily GRV**: 1. day 138 ± 100 2. day 136 ± 115 3. day 114 ± 91 4. day 117 ± 114 5. day 97 ± 72 **mean daily volume ratio (%):** 80.8 ± 9.6
[54]	Xi, 2017	**Episodes of hypoglycemia** 13/63 (20.6)	**Episodes of hypoglycemia** 5/62 (8.06)	**time to reach full EN**: 9.99 ± 1.91 days	**time to reach full EN**: 13 ± 5.12 days
[50]	Fazilaty, 2018	NR	NR	**energy intake** 1710.5 ± 117 kcal	**energy intake** 1718.2 ± 182.4 kcal
[42]	Freedberg, 2020	NR	NR	**% energy requirement achieved (day 3)**: 58 (24-84)	**% energy requirement achieved (day 3):** 33 (2-52)
[48]	Chen, 2021	**Blood glucose** (mmol/l): day 1 12.1 ± 1.8 day 4 9.7 ± 0.99 day 7 9.11 ± 1.11	**Blood glucose** (mmol/l): day 1 12.1 ± 1.57 day 4 11.9 ± 1.17 day 7 11.5 ± 1.39	**time to achieve the energy target with EN**: 5 (4.25-6) days **amount of energy received (kcal/day**): day 1: 250 (mean) day 4: 1500 (1000-1500) day 7: 1750 (1625-1937)	**time to achieve the energy target with EN**: 7 (6-8.25) days **amount of energy received (kcal):** day 1: 250 (mean) day 4: 1000 (750-1000) day 7: 1500 (1187-1750)

Table S6: Diarrheal outcome

Reference No	Author, year	Definition	Fiber n (%)	Control n (%)
[38]	Hart, 1988	diarrhea score ≥ 12 in a 24h period *patients with diarrhea on any day* *% Diarrhea days per feeding days*	 19/35 (54.3) 66/287 (23)	 19/33 (57.6) 68/297 (22.9)
[39]	Dobb, 1990	diarrhea score based on the frequency, volume and consistency of the stool; diarrhea = daily score > 12	16/45 (35.6)	13/46 (28.2)
[47]	Celaya, 1992	NR	3/17 (17.6)	NR
[35]	Caparrós, 2000	≥ 5 liquid stools in a 24-hour period or an estimated volume ≥ 2000ml/d *number of episodes per 1000 days of enteral nutrition*	5.8	50
[41]	Schultz, 2000	Hart and Dobb diarrhea scale, diarrhea was defined as 2 or more days of diarrhea scores ≥ 12 during study days 3 through 8	11/33 (33.3) [fiber + placebo 6/11 (54.5)] [fiber-free + pectin 4/11 (36.3)] [fiber + pectin 1/11 (9.09)]	 1/11 (9.09)
[43]	Spapen, 2001	Hart and Dobb diarrhea scale, diarrhea was defined as a daily score ≥ 12 *Number of patients with at least 1 day with diarrhea* *Percentage of days with diarrhea per feeding days* *Diarrhea score*	 6/13 (46.2) 8.8 ± 10; 16/148 (10.8) 4.8 ± 6.4	 11/12 (91.2) 32 ± 15.3; 46/146 (31.5) 9.4 ± 10.2
[40]	Rushdi, 2004	NR	NR	NR
[37]	Palmese, 2006	NR	0/42	5/42 (11.9)
[49]	Karakan, 2007	NR	NR	NR
[46]	Spindler-Vesel, 2007	NR	NR	NR
[45]	Chittawatanarat, 2010	Hart and Dobb criteria: daily accumulation score ≥ 12 *number of patients with at least 1 day of diarrhea* *Accumulation diarrhea score* *Mean diarrhea score* *Incidence rate of diarrhea (100 patient-fed day)* *Probability of first diarrhea beginning at day 14th (95% CI)*	 4/17 (23.5) 50.8 ± 32 3.6 ± 2.3 6.7 0.24 (0.1-0.5)	 8/17 (47.1) 87.7 ± 50.7 6.3 ± 3.6 14.8 0.47 (0.3-0.7)
[52]	Zavertailo, 2010	NR	NR	NR
[53]	Aytünür, 2012	≥ 5 watery stools in 24 hours or ≥ 2000ml of watery stool	0/30 (0)	0/30 (0)
[51]	Wang, 2014	NR	NR	NR
[36]	Kamarul Zaman, 2016	Diarrhea is defined using the faecal score of the King's stool chart. A score of ≥ 15 was used to indicate diarrhea. *No of patients with at least one day of diarrhea*	18/35 (55)	18/33 (51)
[44]	Yagmurdur, 2016	Hart and Dobb diarrhea scale, diarrhea was defined as a daily score ≥ 12 *Patients with at least 1 day with diarrhea* *Daily diarrhea score, Day 1* *Daily diarrhea score, Day 2* *Daily diarrhea score, Day 3* *Daily diarrhea score, Day 4* *Daily diarrhea score, Day 5* *Diarrhea score for five days*	 22/60 (36.7) 7.1 ± 7.1 7.1 ± 5.6 7.6 ± 6.1 8.6 ± 6.6 7.3 ± 5.9 7.5 ± 4.7	 38/60 (63.3) 8.5 ± 6.9 8.7 ± 7.5 10.2 ± 8 11.7 ± 7.8 12 ± 8.4 10.2 ± 5.4
[54]	Xi, 2017	NR	7/62 (11.3)	16/63 (25.4)
[50]	Fazilaty, 2018	NR	NR	NR
[42]	Freedberg, 2020	NR	NR	NR
[48]	Chen, 2021	>3 loose or liquid stools per day or an estimated volume > 2000ml/d	2/24 (8.33)	9/22 (40.9)

Table S7: Adverse events and serious adverse events

Reference No	Author, year (Country)	Adverse events			Serious adverse events		
		Definition	Fiber	Control	Definition	Fiber	Control
[38]	Hart, 1988 (Australia)	NR	-	-	NR	-	-
[39]	Dobb, 1990 (Australia)	NR	-	-	NR	-	-
[47]	Celaya, 1992 (Spain)	NR	-	-	NR	-	-
[35]	Caparros, 2000 (Spain)	NR	-	-	NR	-	-
[41]	Schultz, 2000 (USA)	NR	-	-	NR	-	-
[43]	Spapen, 2001 (Belgium)	NR	-	-	NR	-	-
[40]	Rushdi, 2004 (Egypt)	NR	-	-	NR	-	-
[37]	Palmese, 2006 (Italy)	NR	-	-	NR	-	-
[49]	Karakan, 2007 (Turkey)	NR	-	-	NR	-	-
[46]	Spindler-Vesel, 2007 (Slovenia)	NR	-	-	NR	-	-
[45]	Chittawatanarat, 2010 (Thailand)	NR	-	-	NR	-	-
[52]	Zavertailo, 2010 (Russia)	NR	-	-	NR		
[53]	Aytünür, 2012 (Turkey)	NR	-	-	NR	-	-
[51]	Wang, 2014 (China)	gastrointestinal adverse reactions: nausea, vomiting, digestive bleeding, abdominal distension, diarrhea, constipation	6/43 (13.95)	13/43 (30.23)	NR		
[36]	Kamarul Zaman, 2016 (Malaysia)	NR	-	-	NR	-	-
[44]	Yagmurdur, 2016 (Turkey)	NR	-	-	NR	-	-
[54]	Xi, 2017 (China)	NR	-	-	NR	-	-
[50]	Fazilaty, 2018 (Iran)	NR	-	-	NR	-	-
[42]	Freedberg, 2020 (USA)	ascertain untoward health events, graded in terms of severity and relatedness to the study intervention	mild: 10/25 (5 definitely unrelated, 5 unlikely related) moderate: 8/25 (7 definitely unrelated, 1 unlikely related)	mild: 4/20 (2 definitely unrelated, 2 unlikely related) moderate: 7/20 (7 definitely unrelated)	ascertain untoward health events, graded in terms of severity and relatedness to the study intervention	severe: 5/25 (5 definitely unrelated) life threatening: 2/25 (2 definitely unrelated)	severe: 7/20 (7 definitely unrelated) life threatening: 3/20 (3 definitely unrelated)
[48]	Chen, 2021 (China)	No definition	0/24	-	NR	-	-

Table S8: Clinical Trial Registry of ongoing or unpublished studies

No	Trial Registration Number	Country	Title	Last update	Status
1	ChiCTR-INR-17012709	China	The effect of early enteral nutrition intervention on patients with severe infections after cardiac surgery to intestinal microflora and metabolize	October 2, 2017	Recruiting
2	ChiCTR1900021972	China	Multicenter clinical study on the effects of enteral nutrition with pectin dietary fiber solution in ICU patients.	March 25, 2019	Not yet recruiting
3	NCT03153397	USA	Effect of Prebiotic Fiber- Enriched (scFOS) Enteral Feeding on the Microbiome in Neurological Injury Trauma Patients (PreFEED Microbiome Trial)	June 4, 2021	Completed, data not published yet
4	NCT04438473	China	Pectin Supplemented Enteral Feedings in Critically Ill Patients	July 15, 2021	Withdrawn
5	ChiCTR2300072211	China	A clinical controlled study of pectin "semi-solidification" for improving tolerance to enteral nutrition	July 25, 2023	Recruitment completed

Table S9: List of excluded studies after full-text review with reasons

No	Reason for exclusion	Reference
1	Wrong study population (Patients < 16 years of age included)	Olguin F, Araya M, Hirsch S, Brunser O, Ayala V, Rivera R, Gotteland M. Prebiotic ingestion does not improve gastrointestinal barrier function in burn patients. Burns. 2005 Jun;31(4):482-8. doi: 10.1016/j.burns.2004.11.017
2	Wrong intervention/control group (enteral vs. combined vs. parenteral nutrition)	Elke G, Kuhnt E, Ragaller M, Schadler D, Frerichs I, Brunkhorst FM, et al. Enteral nutrition is associated with improved outcome in patients with severe sepsis: a secondary analysis of the VISEP trial. Med Klin Intensivmed Notfallmed. (2013) 108:223–33. doi: 10.1007/s00063-013-0224-4
3	Wrong intervention/control group (enteral vs. combined vs. parenteral nutrition)	Fan M-C,Qiao-ling W, Wei F, Yun-xia J, Lian-di L, Sun P, et al. Early enteral combined with parenteral nutrition treatment for severe traumatic brain injury: effects on immune function, nutritional status and outcomes. Chin MedSci J. (2016) 31:213–20. doi: 10.1016/S1001-9294(17)30003-2
4	Wrong intervention and control group (many combined interventions vs. Total parenteral nutrition)	Sun B, Gao Y, Xu J, Zhou XL, Zhou ZQ, Liu C, et al. Role of individually staged nutritional support in the management of severe acute pancreatitis. Hepatobil Pancreat Dis Int. (2004) 3:458–63
5	Wrong intervention (synbiotics)	López de Toro Martín-Consuegra I, et al. Influencia de los simbióticos en la disfunción multiorgánica: ensayo aleatorizado y controlado. Med Clin (Barc). 2014. http://dx.doi.org/10.1016/j.medcli.2013.09.046
6	Wrong intervention (synbiotic)	Jain PK, McNaught CE, Anderson AD, MacFie J, Mitchell CJ. Influence of synbiotic containing Lactobacillus acidophilus La5, Bifidobacterium lactis Bb 12, Streptococcus thermophilus, Lactobacillus bulgaricus and oligofructose on gut barrier function and sepsis in critically ill patients: a randomised controlled trial. Clin Nutr 2004;23:467–75
7	Wrong intervention (synbiotic)	Kanazawa H, Nagino M, Kamiya S, et al. Synbiotics reduce postoperative infectious complications: a randomized con trolled trial in biliary cancer patients undergoing hepatectomy. Langenbecks Arch Surg 2005;390:104–13
8	Wrong intervention (synbiotic)	Rayes N, Hansen S, Seehofer D, et al. Early enteral supply of f iber and Lactobacilli versus conventional nutrition: a con trolled trial in patients with major abdominal surgery. Nutrition 2002;18:609–15
9	Wrong intervention (synbiotic)	Rayes N, Seehofer D, Theruvath T, et al. Supply of pre- and probiotics reduces bacterial infection rates after liver trans plantation—a randomized, double-blind trial. Am J Transplant 1995;5:125–30
10	Wrong intervention (synbiotic)	Kotzampassi K, Giamarellos-Bourboulis EJ, Voudouris A, Kazamias P, Eleftheriadis E. Benefits of a synbiotic formula (Synbiotic 2000Forte) in critically ill trauma patients: earlyresults of a randomized controlled trial. World J Surg. (2006) 30:1848–55. doi: 10.1007/s00268-005-0653-1
11	Wrong intervention (synbiotic)	Sramek V, Dadak L, Stouracova M, Stetka P, Kyr M, Ticha A, et al. Impact of addition of synbiotics (Synbiotic (2000). Forte) to enteral nutrition on the course of MODS, occurrence of sepsis, immune status and gut function in long-term critically ill patients. Anesteziol Intenzivni Med. (2007) 18:157–63
12	Wrong intervention (synbiotic)	Giamarellos-Bourboulis EJ, Bengmark S, Kanellakopoulou K, Kotzampassi K. Pro- and synbiotics to control inflammation and infection in patients with multiple injuries. J Trauma. (2009) 67:815–21. doi: 10.1097/TA.0b013e31819d979e
13	Wrong intervention (synbiotic)	Hayakawa M, Asahara T, Ishitani T, Okamura A, Nomoto K, Gando S. Synbiotic therapy reduces the pathological gram-negative rods caused by an increased acetic acid concentration in the gut. Digest Dis Sci. (2012) 57:2642–9. doi: 10.1007/s10620-012-2201-9
14	Wrong intervention (probiotic), Abstract only	Gomersall CD, Joynt GM, Leung P, Tan P, Bengmark S. Does routine administration of probiotics improve outcome of critically ill patients? ANZCA ASM 2006.
15	Wrong intervention (probiotic), Abstract only	Malian M, Reichenbach R, Peck A, Pamukov N. Probiotic supplementation in critical care. Crit Care Med. (2012) 40:1–328. doi: 10.1097/01.ccm.0000425300.89190.4b
16	Wrong intervention (Probiotic)	Bleichner G, Blehaut H, Mentec H, Moyse D. Saccharomyces boulardii prevents diarrhea in critically ill tube-fed patients. Intensive care medicine. 1997;23(5):517–23. https://doi.org/10.1007/s001340050367
17	Wrong intervention (Probiotic)	Frohmader TJ, Chaboyer WP, Robertson IK, Gowardman J. Decrease in frequency of liquid stool in enterally fed critically ill patients given the multispecies probiotic VSL#3: a pilot trial. Am J Crit Care. 2010;19(3):e1–11. https://doi.org/10.4037/ajcc2010976
18	Wrong intervention (Probiotic)	Barraud D, Blard C, Hein F, Marcon O, Cravoisy A, Nace L, et al. Probiotics in the critically ill patient: a double blind, randomized, placebo-controlled trial. Intensive Care Med. 2010;36(9):1540–7. https://doi.org/10.1007/s00134-010-1 927-0
19	Wrong intervention (Probiotic)	Morrow LE, Kollef MH, Casale TB. Probiotic prophylaxis of ventilator associated pneumonia: a blinded, randomized, controlled trial. Am J Respir Crit Care Med. 2010;182(8):1058–64. https://doi.org/10.1164/rccm.200912-1 853OC
20	Wrong intervention (Probiotic)	Sanaie S, Ebrahimi-Mameghani M, Hamishehkar H, Mojtahedzadeh M, Mahmoodpoor A. Effect of a multispecies Probiotic on inflammatory markers in critically ill patients: a randomized, double-blind, placebo controlled trial. J Res Med Sci. 2014;19(9):827–33

21	Wrong intervention (Probiotic)	Malik AA, Rajandram R, Tah PC, Hakumat-Rai VR, Chin KF. Microbial cell preparation in enteral feeding in critically ill patients: A randomized, double blind, placebo-controlled clinical trial. J Crit Care. 2016;32:182–8. https://doi. org/10.1016/j.jcrc.2015.12.008
22	Wrong intervention (Probiotic)	Shimizu K, Yamada T, Ogura H, Mohri T, Kiguchi T, Fujimi S, Asahara T, Yamada T, Ojima M, Ikeda M, Shimazu T. Synbiotics modulate gut microbiota and reduce enteritis and ventilator-associated pneumonia in patients with sepsis: a randomized controlled trial. Crit Care. 2018;22(1):239. https://doi.org/10.1186/s13054-018-2167-x
23	Wrong intervention (probiotic)	Li, Y. M. (2007). Adjuvant therapy for probiotics in patients with severe acute pancreatitis: an analysis of 14 cases. World Chin. J. Digestol. 15, 302–304. doi: 10.3969/j.issn.1009-3079.2007.03.019
24	Wrong intervention (probiotic)	Besselink, M. G., van Santvoort, H. C., Buskens, E., Boermeester, M. A., van Goor, H., Timmerman, H. M., et al. (2008). Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet 371, 651–659. doi: 10.1016/S0140-6736(08)60207-X
25	Wrong intervention (probiotic)	Wu, X. G., and Zhang, Q. C. (2009). Adjuvant therapy for probiotics in patients with severe acute pancreatitis with hepatic lesion: an analysis of 27 cases. Clin. Med. 29, 51–52
26	Wrong intervention (probiotic)	Lata, J., Jurankova, J., Stiburek, O., Pribramska, V., Senkyrik, M., and Vanasek, T. (2010). Probiotics in acute pancreatitis- A randomised, placebo-controlled, double-blind study. Vnitr. Lek. 56, 111–114
27	Wrong intervention (probiotic)	Cui, L.-H., Wang, X.-H., Peng, L.-H., Yu, L., and Yang, Y.-S. (2013). The effects of early enteral nutrition with addition of probiotics on the prognosis of patients suffering from severe acute pancreatitis, Chinese critical care medicine. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 25, 224–228. doi: 10.3760/cma.j.issn.2095-4352.2013.04.011
28	Wrong intervention (probiotic)	Wang, G., Wen, J., Xu, L., Zhou, S., Gong, M., Wen, P., et al. (2013). Effect of enteral nutrition and ecoimmunonutrition on bacterial translocation and cytokine production in patients with severe acute pancreatitis. J. Surg. Res. 183, 592–597. doi: 10.1016/j.jss.2012.12.010
29	Wrong intervention (probiotic)	Zhu, Y. M., Lin, S., Dang, X. W., Wang, M., Li, L., Sun, R. Q., et al. (2014). Effects of probiotics in treatment of severe acute pancreatitis. World Chin. J. Digestol. 22, 5013–5017. doi: 10.11569/wcjd.v22.i32.5013
30	Wrong intervention (probiotic)	Li, J., Wang, J., and Xu, Y. Q. (2014). Effect of early enteral nutrition with Bifico on levels of inflammatory mediators in plasma of patients with severe acute pancreatitis. World Chin. J. Digestol. 22, 5609–5614. doi: 10.11569/wcjd.v22.i36.5609
31	Wrong intervention (probiotic)	Wu,P., Yu, Y., Li, L., and Sun, W. (2017). Effect and safety of probiotics combined early enteral nutrition on severe acute pancreatitis patients. Biomed. Res. 28, 1403–1407
32	Wrong intervention (probiotic)	Klarin B, Johansson ML, Molin G, Larsson A, Jeppsson B. Adhesion of the probiotic bacterium Lactobacillus plantarum 299v onto the gut mucosa in critically ill patients: a randomised open trial. Crit Care 2005;9:R285–93
33	Wrong intervention (probiotic)	McNaught CE, Woodcock NP, Anderson AD, MacFie J. A prospective randomised trial of probiotics in critically ill patients. Clin Nutr 2005;24:211–9
34	Wrong intervention (probiotic)	Morrow LE, Kollef MH, Bowers JB, Casale TB. Probiotic manipulation of the native flora in critically ill patients: an opportunity for ventilator-associated pneumonia prophylaxis? Chest. (2005) 128:144S. doi: 10.1378/chest.128.4_MeetingAbstracts.144S
35	Wrong intervention (probiotic)	Alberda C, Gramlich L, Meddings J, Field C, McCargar L, Kutsogiannis D, et al. Effects of probiotic therapy in critically ill patients: a randomized, double-blind, placebo-controlled trial. Am J Clin Nutr. (2007) 85:816–23. doi: 10.1093/ajcn/85.3.816
36	Wrong intervention (probiotic)	Forestier C, Guelon D, Cluytens V, Gillart T, Sirot J, De Champs C. Oral probiotic and prevention of Pseudomonas aeruginosa infections: a randomized, double-blind, placebo-controlled pilot study in intensive care unit patients. Critical care. (2008) 12:R69. doi: 10.1186/cc6907
37	Wrong intervention (probiotic)	Klarin B, Wullt M, Palmquist I, Molin G, Larsson A, Jeppsson B. Lactobacillus plantarum 299v reduces colonisation of Clostridium difficile in critically ill patients treated with antibiotics. Acta Anaesthesiol Scand. (2008) 52:1096–102. doi: 10.1111/j.1399-6576.2008.01748.x
38	Wrong intervention (probiotic)	Tan M, Zhu JC, Du J, Zhang LM, Yin HH. Effects of probiotics on serum levels of Th1/Th2 cytokine and clinical outcomes in severe traumatic brain injured patients: a prospective randomized pilot study. Crit Care. (2011) 15:R290. doi: 10.1186/cc10579
39	Wrong intervention (probiotic)	Tan M, Xiao-lan L, Jun-wei D, Hua P, Jing-ci Z. Effects of probiotics on blood glucose levels and clinical outcomes in patients witn severe craniocerebral trauma. Chin Crit Care Med. (2013) 25:627–30. doi: 10.3760/cma.j.issn.2095-4352.2013.10.012
40	Wrong intervention (probiotic)	Rongrungruang Y, Krajangwittaya D, Pholtawornkulchai K, Tiengrim S, Thamlikitkul V. Randomized controlled study of probiotics containing Lactobacillus casei (Shirota strain) for prevention of ventilator-associated pneumonia. J Med Assoc Thai. (2015) 98:253–9
41	Wrong intervention (probiotic)	Zarinfar N, Sharafkhah M, Amiri M, Rafeie M. Probiotic effects in prevention from ventilator-associated pneumonia. Koomesh. (2016) 7:803–13
42	Wrong intervention (probiotic)	Zeng J, Wang CT, Zhang FS, Qi F, Wang SF, Ma S, et al. Effect of probiotics on the incidence of ventilator-associated pneumonia in critically ill patients: a randomized controlled multicenter trial. Intens Care Med. (2016) 42:1018 28. doi: 10.1007/s00134-016-4303-x
43	Wrong intervention (probiotic)	Alberda C, Marcushamer S, Hewer T, Journault N, Kutsogiannis D. Feasibility of a Lactobacillus casei drink in the intensive care unit for prevention of antibiotic associated diarrhea and Clostridium difficile. Nutrients. (2018) 10:539. doi: 10.3390/nu10050539
44	Wrong intervention (probiotic)	Mahmoodpoor A, Hamishehkar H, Asghari R, Abri R, Shadvar K, Sanaie S. Effect of a probiotic preparation on ventilator-associated pneumonia in critically ill patients admitted to the intensive care unit: a prospective double-blind randomized controlled trial. Nutr Clin Pract. (2019) 34:156–62. doi: 10.1002/ncp.10191
45	Wrong intervention (probiotic)	Li YM. Adjuvant therapy for probiotics in patients with se vere acute pancreatitis: An analysis of 14 cases. Shijie Huaren Xiaohua Zazhi 2007; 15: 302-304
46	Wrong intervention (probiotic)	Wu XG, Zhang QC. Adjuvant therapy for probiotics in pa tients with severe acute pancreatitis with hepatic lesion: an analysis of 27 cases. Clin Med 2009; 29: 51-52

47	Wrong intervention (many combined interventions but no fiber)	Kudsk KA, Minard G, Croce MA, Brown RO, Lowrey TS, Pritchard FE, et al. A randomized trial of isonitrogenous enteral diets after severe trauma: an immune-enhancing diet reduces septic complications. Ann Surg. (1996) 224:531–43. doi: 10.1097/00000658-199610000-00011
48	Wrong intervention (glutamine + probiotics)	Falcão De Arruda IS, De Aguilar-Nascimento JE. Benefits of early enteral nutrition with glutamine and probiotics in brain injury patients. Clin Sci. (2004) 106:287–92. doi: 10.1042/CS20030251
49	Wrong control group (fiber-containing formula vs. fiber-containing formula)	van Steen SC, Rijkenberg S, Sechterberger MK, DeVries JH, van der Voort PHJ. Glycemic Effects of a Low-Carbohydrate Enteral Formula Compared With an Enteral Formula of Standard Composition in Critically Ill Patients: An Open-Label Randomized Controlled Clinical Trial. JPEN J Parenter Enteral Nutr. 2018 Aug;42(6):1035-1045. doi: 10.1002/jpen.1045
50	Wrong control group (fiber-containing formula + fiber vs. fiber-containing formula + placebo)	Majid HA, Cole J, Emery PW, Whelan K. Additional oligofructose/inulin does not increase faecal bifidobacteria in critically ill patients receiving enteral nutrition: a randomised controlled trial. Clin Nutr. 2014 Dec;33(6):966-72. doi: 10.1016/j.clnu.2013.11.008
51	Wrong control group (enteral vs. parenteral nutrition)	Petrov MS, Kukosh MV, Emelyanov NV. A randomized controlled trial of enteral versus parenteral feeding in patients with predicted severe acute pancreatitis shows a significant reduction in mortality and in infected pancreatic complications with total enteral nutrition. Digesti Surg. (2006) 23:336–44; discussion 344–335. doi: 10.1159/000097949
52	Wrong control group (enteral vs. parenteral nutrition)	Abdulmeguid AM, Hassan A. Enteral versus parenteral nutrition in mechanically ventilated patients. Neurol Croatica. (2007) 56:15–24
53	Wrong control group (enteral vs. parenteral nutrition)	Casas M, Mora J, Fort E, Farré A, Aracil C, Busquets D, et al. Total enteral nutrition vs. total parenteral nutrition in patients with severe acute pancreatitis. Rev Esp Enferm Dig. (2007) 99:264–9. doi: 10.4321/S1130-01082007000500004
54	Wrong control group (enteral vs. parenteral nutrition)	Doley RP, Wig TDYJ, Kochhar R, Singh G, Bharathy KGS, Kudari A, et al. Enteral nutrition in severe acute pancreatitis. J Pancreas. (2009) 10:157–62. doi: 10.1115/1.1456090
55	Wrong control group (enteral vs. parenteral nutrition)	Moses V, Mahendri NV, John G, Peter JV, Ganesh A. Early hypocaloric enteral nutritional supplementation in acute organophosphate poisoning a prospective randomized trial. Clin Toxicol. (2009) 47:419–24. doi: 10.1080/15563650902936664
56	Wrong control group (enteral vs. parenteral nutrition)	Fu Y-H, Jian-Bo W, Gui-Liang W, Ping W, Min G, Ming H, et al. Effect of enteral nutrition on cytokine production and plasma endotoxin in patients with severe acute pancreatitis. World Chin J Digestol. (2015) 23:1174. doi: 10.11569/wcjd.v23.i7.1174
57	Wrong control group (enteral vs. parenteral nutrition)	Kim JM, Joh JW, Kim HJ, Kim SH, Rha M, Sinn DH, et al. Early enteral feeding after living donor liver transplantation prevents infectious complications: a prospective pilot study. Medicine. (2015) 94:e1771. doi: 10.1097/MD.0000000000001771
58	Wrong control group (enteral vs. parenteral nutrition)	Reignier J, Boisramé-Helms J, Brisard L, Lascarrou J-B, Ait Hssain A, Anguel N, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open label, parallel-group study (NUTRIREA-2). Lancet. (2018) 391:133–43. doi: 10.1016/S01406736(17)32146-3
59	Wrong control group (critically ill patients vs. healthy individuals)	Hong-Guang Lu, Yu-Be Shi, Li-Ming Zhao, Chunxue Bai & Xiangdong Wang (2008) Role of enteral ebselen and ethylhydroxyethyl cellulose in pancreatitis-associated multiple-organ dysfunction in humans, Journal of Organ Dysfunction, 4:1, 43-50, DOI: 10.1080/17471060701486209
60	Systematic review, Not critically ill patients	Gurusamy KS, Nagendran M, Davidson BR. Methods of preventing bacterial sepsis and wound complications a#er liver transplantation. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD006660. DOI: 10.1002/14651858.CD006660.pub3
61	Systematic review, Not critically ill patients	Poropat G, Giljaca V, Hauser G, Štimac D. Enteral nutrition formulations for acute pancreatitis. Cochrane Database of Systematic Reviews 2015, Issue 3. Art. No.: CD010605. DOI: 10.1002/14651858.CD010605.pub2
62	Systematic review - included studies are reviewed	Hajipour A, Afsharfar M, Jonoush M, et al. The effects of dietary fiber on commoncomplications in critically ill patients; with a special focus on viral infections; a systematic reveiw. Immun Inflamm Dis. 2022;10:e613. doi:10.1002/iid3.613
63	Systematic review - included studies are reviewed	Li C, Liu L, Gao Z, Zhang J, Chen H, Ma S, Liu A, Mo M, Wu C, Chen D, Liu S, Xie J, Huang Y, Qiu H and Yang Y (2021) Synbiotic Therapy Prevents Nosocomial Infection in Critically Ill Adult Patients: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials Based on a Bayesian Framework. Front. Med. 8:693188. doi: 10.3389/fmed.2021.693188
64	Systematic review - included studies are reviewed	Seifi N, Jafarzadeh Esfahani A, Sedaghat A, Rezvani R, Khadem-Rezaiyan M, Nematy M, Safarian M. Effect of gut microbiota modulation on feeding tolerance of enterally fed critically ill adult patients: a systematic review. Syst Rev. 2021 Apr 2;10(1):95. doi: 10.1186/s13643-021-01633-5
65	Systematic review - included studies are reviewed	Tian X, Pi Y-P, Liu X-L, Chen H and Chen W-Q (2018) Supplemented Use of Pre-, Pro-, and Synbiotics in Severe Acute Pancreatitis: An Updated Systematic Review and Meta-Analysis of 13 Randomized Controlled Trials. Front. Pharmacol. 9:690. doi: 10.3389/fphar.2018.00690
66	Systematic review - included studies are reviewed	Watkinson PJ, Barber VS, Dark P, Young JD. The use of pre- pro- and synbiotics in adult intensive care unit patients: systematic review. Clin Nutr. 2007 Apr;26(2):182-92. doi: 10.1016/j.clnu.2006.07.010
67	Systematic review - included studies are reviewed	Yang G, Wu XT, Zhou Y, Wang YL. Application of dietary fiber in clinical enteral nutrition: A meta-analysis of randomized controlled trials. World J Gastroenterol 2005; 11(25): 3935-3938
68	Systematic review - included studies are reviewed	Zhang MM, Cheng JQ, Lu YR, Yi ZH, Yang P, Wu XT. Use of pre-, pro- and synbiotics in patients with acute pancreatitis: A meta-analysis. World J Gastroenterol 2010; 16(31): 3970-3978

70	Not RCT, not critically ill	Buil-Cosiales P, Zazpe I, Toledo E, et al. Fiber intake and all cause mortality in the Prevención con Dieta Mediterránea (PREDIMED) study. Am J Clin Nutr. 2014;100(6):1498-1507
71	Not RCT, not critically ill	Berthon BS, Macdonald-Wicks LK, Gibson PG, Wood LG. Investigation of the association between dietary intake, disease severity and airway inflammation in asthma. Respirology. 2013;18(3):447-454
72	Not RCT, not critically ill	Halnes I, Baines KJ, Berthon BS, MacDonald-Wicks LK, Gibson PG, Wood LG. Soluble fibre meal challenge reduces airway inflammation and expression of GPR43 and GPR41 in asthma. Nutrients. 2017;9(1):57
73	Not RCT, not critically ill	Katagiri R, Goto A, Sawada N, et al. Dietary fiber intake and total and cause-specific mortality: the Japan Public Health Center-based prospective study. Am J Clin Nutr. 2020;111(5): 1027-1035
74	not RCT, not critically ill	Park Y, Subar AF, Hollenbeck A, Schatzkin A. Dietary fiber intake and mortality in the NIH-AARP diet and health study. Arch Intern Med. 2011;171(12):1061-1068
75	Not RCT, not critically ill	Salmean YA, Segal MS, Langkamp-Henken B, Canales MT, Zello GA, Dahl WJ. Foods with added fiber lower serum creatinine levels in patients with chronic kidney disease. J Ren Nutr. 2013;23(2):e29-e32
76	Not RCT (pseudorandomized)	Tuncay P, Arpaci F, Doganay M, Erdem D, Sahna A, Ergun H, Atabey D. Use of standard enteral formula versus enteric formula with prebiotic content in nutrition therapy: A randomized controlled study among neuro-critical care patients. Clin Nutr ESPEN. 2018 Jun;25:26-36. doi: 10.1016/j.clnesp.2018.03.123
77	Not RCT	Chittawatanarat K, Surawang S, Simapaisan P, Judprasong K. Jerusalem Artichoke Powder Mixed in Enteral Feeding for Patients Who have Diarrhea in Surgical Intensive Care Unit: A Method of Preparation and a Pilot Study. Indian J Crit Care Med 2020;24(11):1051–1056
78	Not RCT	FuY,Moscoso DI, Porter J, et al. Relationship between dietary fiber intake and short-chain fatty acid-producing bacteria during critical illness: a prospective cohort study. JPEN J Parenter Enteral Nutr. 2020;44(3):463-471
79	Not RCT	Kooshki AZK, Zarghi A, Rad M, Tabaraie Y. Prebiotic prophylaxis of ventilator-associated pneumonia: a randomized clinical trial. Biomed Res Ther. (2018) 5:2287–95. doi: 10.15419/bmrat.v5i5.442
80	Not critically ill, wrong intervention and control (probiotic vs. Fiber-containing)	Oláh A, Belágyi T, Issekutz A, Gamal ME, Bengmark S. Randomized clinical trial of specific lactobacillus and fibre supplement to early enteral nutrition in patients with acute pancreatitis. Br J Surg 2002; 89: 1103-1107
81	Not critically ill patients	Plaudis, H., Pupelis, G., Zeiza, K., and Boka, V. (2012). Early low volume oral synbiotic/prebiotic supplemented enteral stimulation of the gut in patients with severe acute pancreatitis: a prospective feasibility study. Acta Chir. Belg. 112, 131–138. doi: 10.1080/00015458.2012.11680811
82	Not critically ill patients	Qin HL, Zheng JJ, Tong DN, Chen WX, Fan XB, Hang XM, Jiang YQ. Effect of Lactobacillus plantarum enteral feed ing on the gut permeability and septic complications in the patients with acute pancreatitis. Eur J Clin Nutr 2008; 62: 923-930
83	Not critically ill (both ICU and general medical care units)	Belknap D, Davidson LJ, Smith CR (1997). The effects of psyllium hydrophilic mucilloid on diarrhea in enterally fed patients. Heart & Lung, 26(3), 229–237. DOI: 10.1016/s0147-9563(97)90060-1
84	Not critically ill	Chen C, Zeng Y, Xu J, et al. Therapeutic effects of soluble dietary fiber consumption on type 2 diabetes mellitus. Exp Ther Med. 2016;12(2):1232-1242
85	Not critically ill	Yasukawa Z, Inoue R, Ozeki M, Okubo T, Takagi T, Honda A, Naito Y. Effect of Repeated Consumption of Partially Hydrolyzed Guar Gum on Fecal Characteristics and Gut Microbiota: A Randomized, Double-Blind, Placebo-Controlled, and Parallel-Group Clinical Trial. Nutrients. 2019 Sep 10;11(9):2170. doi: 10.3390/nu11092170
86	not critically ill	McLoughlin R, Berthon BS, Rogers GB, et al. Soluble fibre supplementation with and without a probiotic in adults with asthma: a 7-day randomised, double blind, three way cross over trial. EBioMedicine. 2019;46:473-485
87	Not critically ill	Jakobsen LH, Wirth R, Smoliner C, Klebach M, Hofman Z, Kondrup J. Gastrointestinal tolerance and plasma status of carotenoids, EPA and DHA with a fiber-enriched tube feed in hospitalized patients initiated on tube nutrition: randomized controlled trial. Clin Nutr. 2017;36(2):380-388
88	Not critically ill	Homann HH, Kemen M, Fuessenich C, Senkal M, Zumtobel V. Reduction in diarrhea incidence by soluble fiber in patients receiving total or supplemental enteral nutrition. J Parenter Enteral Nutr 1994; 18: 486-490
89	Not critically ill	Khalil L, Ho KH, Png D, Ong CL. The effect of enteral fibre containing feeds on stool parameters in the post-surgical period. Singapore Med J 1998; 39: 156-159
90	No relevant outcome	Lee JG, Kim YS, Lee YJ, Ahn HY, Kim M, Kim M, et al. Effect of Immune-Enhancing Enteral Nutrition Enriched with or without Beta-Glucan on Immunomodulation in Critically Ill Patients. Nutrients. 2016;8(6)
91	Elective surgery patients, wrong intervention (many combined interventions but no fiber)	Braga M, Vignali A, Gianotti L, Cestari A, Profili M, Di Carlo V. Benefits of early postoperative enteral feeding in cancer patients. Infusionsther Transfusionsmed. (1995) 22:280–4. doi: 10.1159/000223143
92	Elective surgery patients	Zhao R, WangY, HuangY, et al. Effects of fiber and probiotics on diarrhea associated with enteral nutrition in gastric cancer patients: a prospective randomized and controlled trial. Medicine (Baltimore). 2017;96(43):e8418

Table S10: Canadian Critical Care Nutrition Methodological Scoring

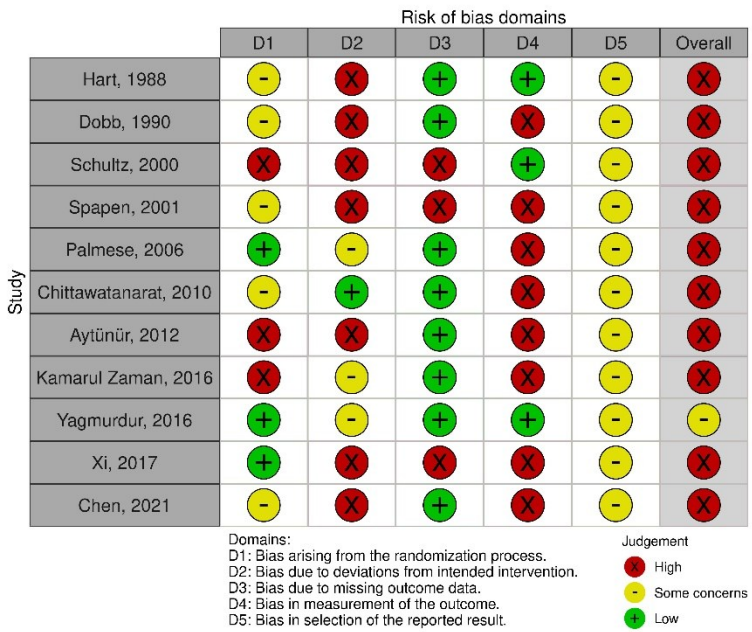
Reference No	Author, year	Concealed Randomization	Intention-to-treat Analysis	Blinding	Patient Selection	Comparability of groups at baseline	Extent of Follow-up	Description of treatment protocol	Description of treatment co-interventions	Objectivity of the definition of outcomes	Total score (max. 14)	Level*
[38]	Hart, 1988	1	0	2	0	1	1	0	2	2	9	2
[39]	Dobb, 1990	1	0	1	0	1	1	0	0	2	6	2
[47]	Celaya, 1992	1	2	0	0	1	1	0	0	0	5	2
[35]	Caparrós, 2000	2	0	0	0	1	1	1	0	2	7	2
[41]	Schultz, 2000	1	0	2	0	0	1	0	0	2	6	2
[43]	Spapen, 2001	1	0	1	0	1	1	0	0	2	6	2
[40]	Rushdi, 2004	2	0	0	1	0	1	0	2	1	7	2
[37]	Palmese, 2006	2	2	0	0	1	1	0	0	0	6	2
[49]	Karakan, 2007	1	2	2	1	1	1	0	0	0	8	2
[46]	Spindler-Vesel, 2007	1	0	0	0	0	1	0	0	0	2	2
[45]	Chittawatanarat, 2010	1	2	1	0	1	1	0	1	1	8	2
[52]	Zavertailo, 2010	2	2	0	0	1	1	0	1	2	9	2
[53]	Aytünür, 2012	1	2	0	0	0	1	0	1	2	7	2
[51]	Wang, 2014	1	2	1	0	1	1	0	0	0	6	2
[36]	Kamarul Zaman, 2016	1	2	0	1	1	0	0	0	2	7	2
[44]	Yagmurdur, 2016	2	2	1	0	1	1	1	0	2	10	2
[54]	Xi, 2017	2	0	0	0	1	0	1	1	0	5	2
[50]	Fazilaty, 2018	2	0	2	0	0	1	0	0	1	6	2
[42]	Freedberg, 2020	1	0	0	0	1	1	0	1	1	5	2
[48]	Chen, 2021	2	0	1	0	0	1	0	0	2	6	2
										Median	**6**	

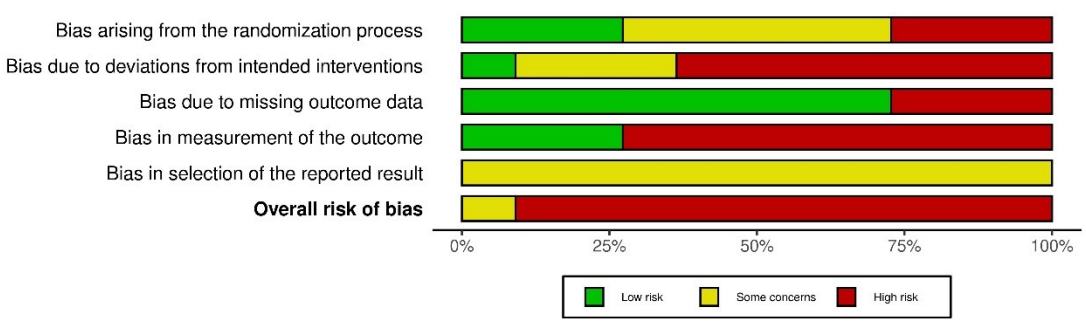
* A trial was considered a level 1 study if all the following criteria were fulfilled: 1) concealed randomization, 2) double-blinded and 3) conduction of intention-to-treat-analysis. If any one of the above characteristics was unfulfilled, it was considered as a level 2 study.

Figure S1: ROB2 traffic light and summary plots

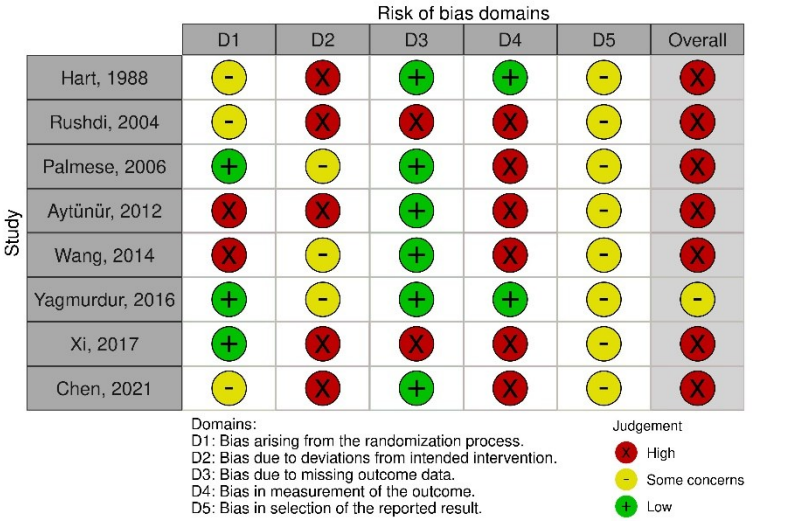
1a) Overall mortality

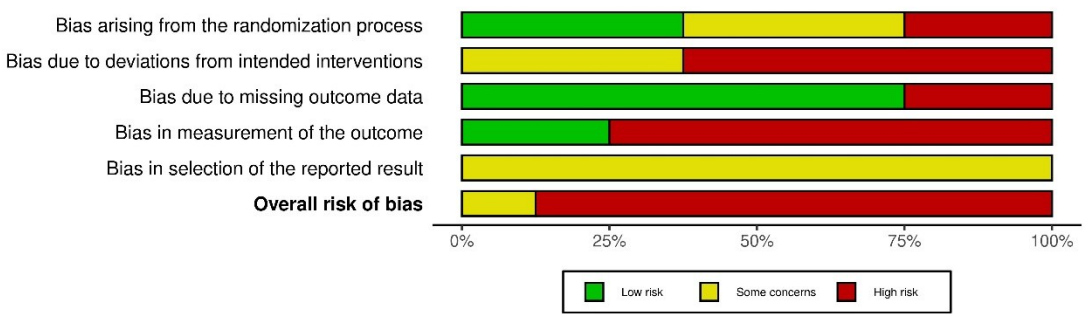
1b) Diarrhea


Risk of bias domains
D1
D2
D3
D4
D5
Overall
Study
Hart, 1988
Dobb, 1990
Schultz, 2000
Spapen, 2001
Palmese, 2006
Chittawatanarat, 2010
Aytünür, 2012
Kamarul Zaman, 2016
Yagmurdur, 2016
Xi, 2017
Chen, 2021
Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.
Judgement
High
Some concerns
Low

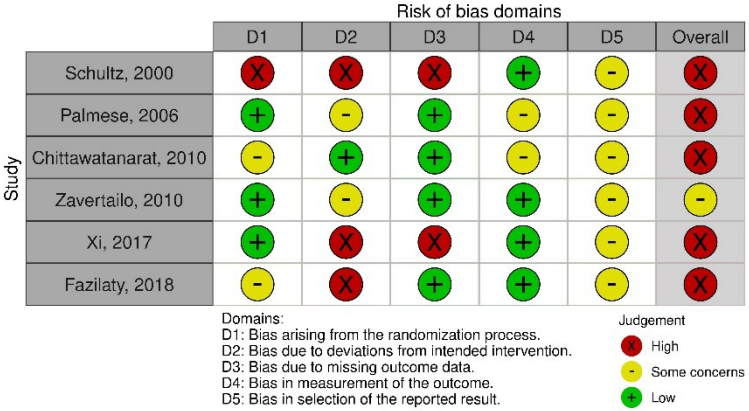

Bias arising from the randomization process
Bias due to deviations from intended interventions
Bias due to missing outcome data
Bias in measurement of the outcome
Bias in selection of the reported result
Overall risk of bias
0%
25%
50%
75%
100%
Low risk
Some concerns
High risk

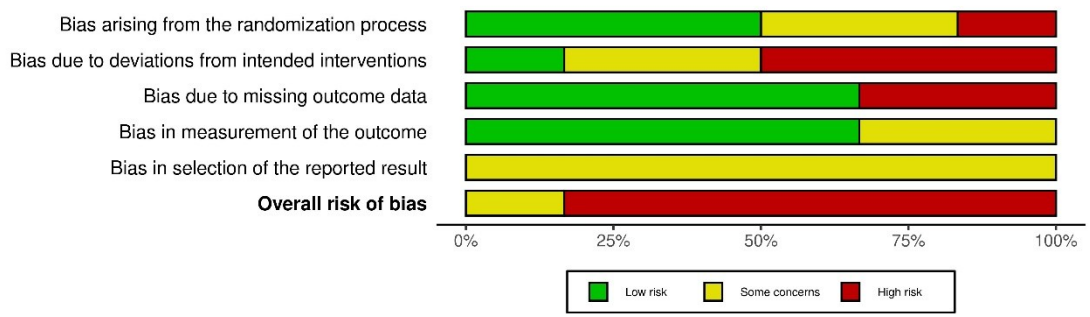
1c) Other GI complications



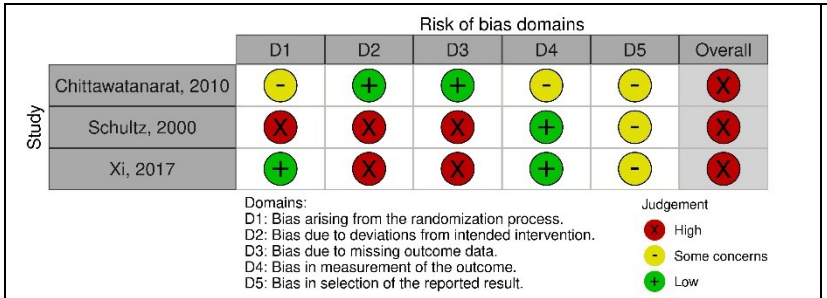


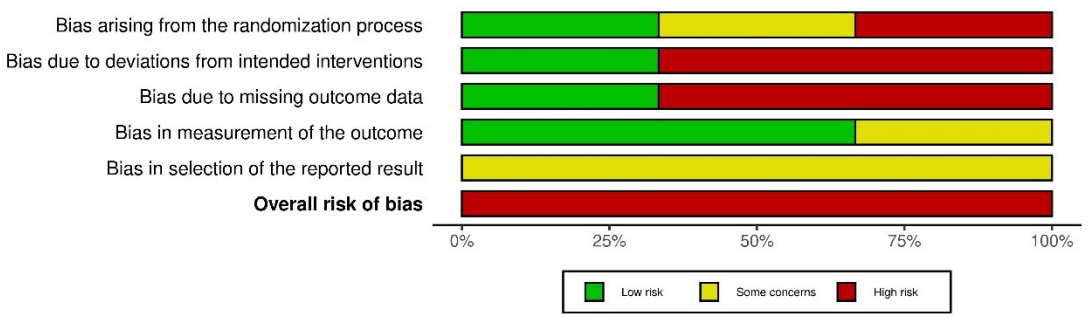
1d) ICU LOS



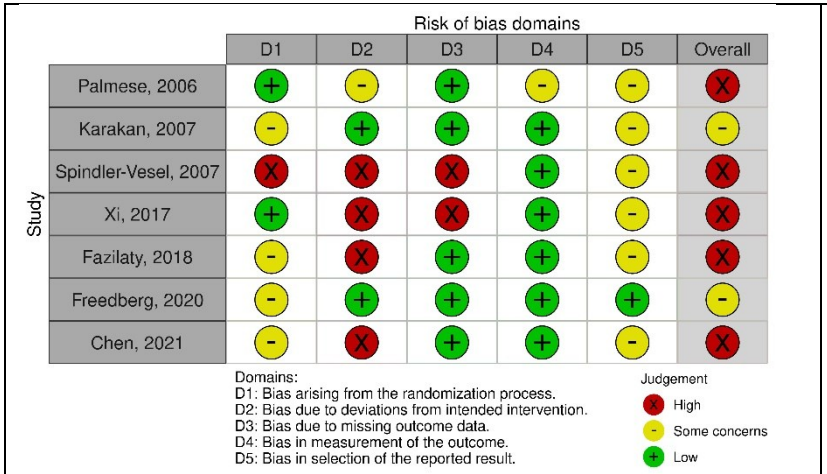


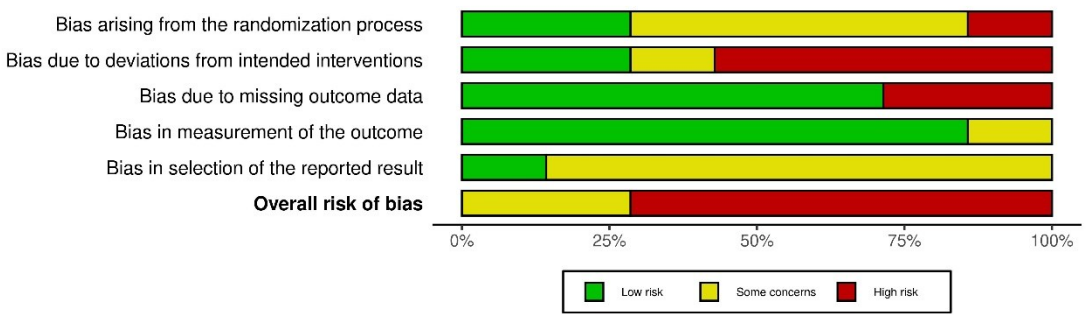
1e) Hospital LOS



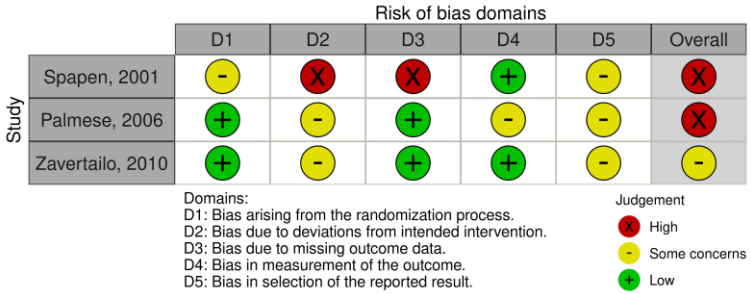


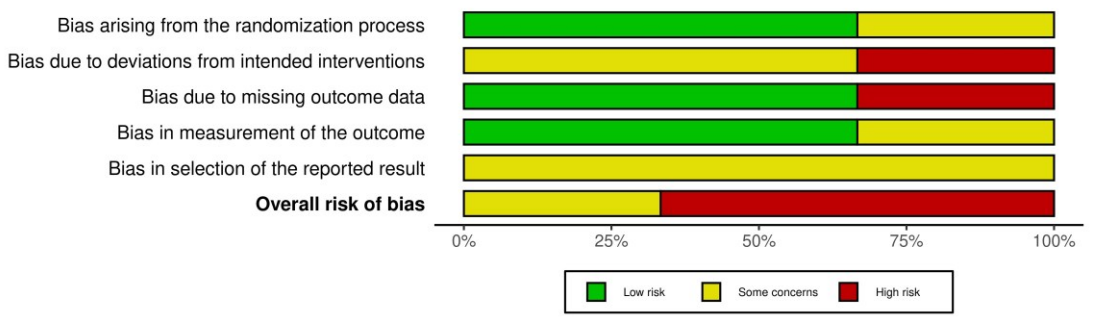
1f) Infectious complications



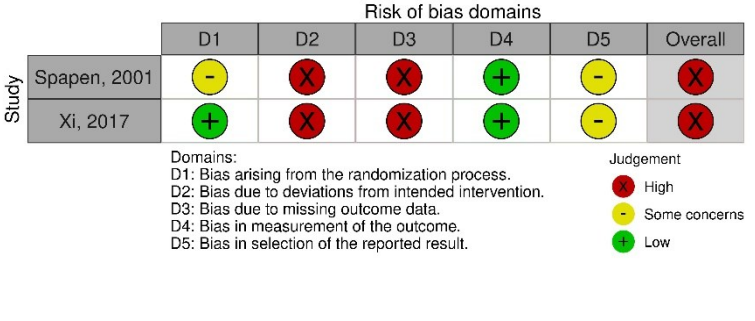


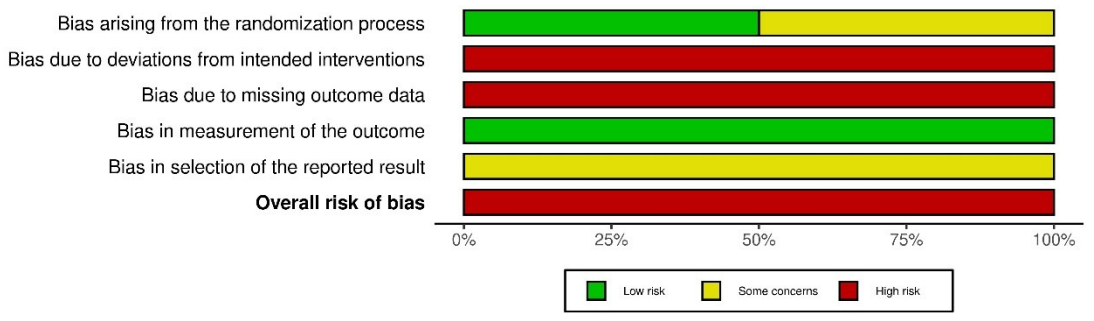
1g) Duration of mechanical ventilation





1h) Time to reach target energy needs





PART 3: Results of the meta-analyses and subgroup analyses

PART 3A: Subgroup analyses

Table S11: Summary of the results of subgroup analyses

Outcome/ Subgroups	Trials	N (fiber/control)	I^2 (%)	RR/MD (95% CI)	p-value	Test for subgroup difference
Mortality	12	399/403	0	0.66 [0.47, 0.92]	0.01	
Published before 2000	1	17/18	-	0.85 [0.27, 2.64]	0.77	$Chi^2 = 0.21$, df = 1 (p = 0.65), $I^2 = 0\%$
Published after 2000	11	382/385	0	0.64 [0.46, 0.91]	0.01	
Fermentable fiber	7	207/235	0	0.63 [0.35, 1.14]	0.13	$Chi^2 = 0.18$, df = 2 (p = 0.92), $I^2 = 0\%$
Non-fermentable fiber	0			-		
Mixed fiber	4	177/153	0	0.69 [0.45, 1.04]	0.08	
Unspecified	1	15/15	-	0.50 [0.11, 2.33]	0.38	
Viscous fiber	2	82/83	0	0.29 [0.06, 1.33]	0.11	$Chi^2 = 1.37$, df = 3 (p = 0.71), $I^2 = 0\%$
Non-viscous fiber	5	125/152	0	0.72 [0.39, 1.36]	0.32	
Mixed fiber	4	177/153	0	0.69 [0.45, 1.04]	0.08	
Unspecified	1	15/15	-	0.50 [0.11, 2.33]	0.38	
Soluble fiber	6	190/217	0	0.57 [0.29, 1.13]	0.11	$Chi^2 = 0.36$, df = 2 (p = 0.83), $I^2 = 0\%$
Insoluble fiber	1	17/18	-	0.85 [0.27, 2.64]	0.77	
Mixed fiber	5	192/168	0	0.67 [0.45, 1.00]	0.05	
daily fiber dose < 20 g	4	194/170	0	0.66 [0.45, 0.98]	0.04	$Chi^2 = 0.11$, df = 2 (p = 0.95), $I^2 = 0\%$
daily fiber dose ≥ 20 g	5	147/175	0	0.59 [0.24, 1.44]	0.24	
Unclear	3	58/58	0	0.72 [0.31, 1.65]	0.44	
Low risk of bias	0					
High risk of bias/ some concerns	12					
age < 50 years	8	212/241	0	0.66 [0.36, 1.22]	0.19	$Chi^2 = 0.00$, df = 1 (p = 0.98), $I^2 = 0\%$
age ≥ 50 years	4	187/162	0	0.66 [0.44, 0.98]	0.04	
APACHE II < 17	4	134/164	0	0.74 [0.32, 1.73]	0.49	$Chi^2 = 0.77$, df = 2 (p = 0.68), $I^2 = 0\%$
APACHE II ≥ 17	6	235/209	0	0.68 [0.46, 0.99]	0.04	
Unclear	2	30/30	0	0.40 [0.12, 1.32]	0.13	
Medical ICU	2	23/22	0	0.39 [0.12, 1.26]	0.12	$Chi^2 = 1.17$, df = 3 (p = 0.76), $I^2 = 0\%$
Surgical ICU	2	46/75	0	0.94 [0.23, 3.74]	0.92	
Mixed ICU	2	164/140	0	0.70 [0.46, 1.07]	0.10	
Unclear	6	166/166	0	0.61 [0.31, 1.20]	0.15	
intervention start ≤ 24h	4	99/127	0	0.66 [0.33, 1.33]	0.24	$Chi^2 = 0.04$, df = 2 (p = 0.98), $I^2 = 0\%$
intervention start ≤ 48h	3	204/181	0	0.64 [0.41, 1.00]	0.05	
Unclear	5	96/95	0	0.70 [0.34, 1.42]	0.32	
minimum duration of intervention < 6 days	2	27/27	0	0.50 [0.15, 1.71]	0.27	$Chi^2 = 0.70$, df = 2 (p = 0.71), $I^2 = 0\%$
minimum duration of intervention ≥ 6 days	6	249/226	0	0.63 [0.43, 0.93]	0.02	
Unclear	4	123/150	0	0.84 [0.41, 1.73]	0.64	
co-intervention with immunonutrition	2	164/140	0	0.70 [0.46, 1.07]	0.10	$Chi^2 = 0.24$, df = 1 (p = 0.62), $I^2 = 0\%$
fiber only	10	235/263	0	0.59 [0.34, 1.02]	0.06	
Industry funding	3	152/127	0	0.65 [0.42, 1.01]	0.06	$Chi^2 = 0.34$, df = 2 (p = 0.84), $I^2 = 0\%$
Non-industry funding	4	121/151	0	0.54 [0.22, 1.33]	0.18	
Unclear funding	5	126/125	0	0.74 [0.41, 1.34]	0.32	
Standard formula in control group	8	189/187	0	0.47 [0.24, 0.90]	0.02	$Chi^2 = 1.43$, df = 1 (p = 0.23), $I^2 = 29.9\%$
Non-standard formula in control group	4	210/216	0	0.74 [0.51, 1.09]	0.12	

Outcome/ Subgroups	Trials	N (fiber/control)	I² (%)	RR/MD (95% CI)	p-value	Test for subgroup difference
Diarrhea	11	396/369	51	0.70 [0.51, 0.96]	0.03	
Published before 2000	2	80/79	0	1.04 [0.73, 1.46]	0.84	Chi² = 4.86, df = 1 (p = 0.03), I² = 79.4%
Published after 2000	9	316/290	43	0.59 [0.40, 0.85]	0.005	
Fermentable fiber	7	256/251	57	0.70 [0.47, 1.05]	0.08	Chi² = 3.75, df = 2 (p = 0.15), I² = 46.7%
Non-fermentable fiber	0	-				
Mixed fiber	2	77/77	0	0.57 [0.40, 0.81]	0.002	
Unspecified	2	63/41	-	3.67 [0.53, 25.26]	0.19	
Viscous fiber	2	97/96	66	0.70 [0.32, 1.50]	0.36	Chi² = 3.61, df = 3 (p = 0.31), I² = 16.8%
Non-viscous fiber	5	159/155	64	0.66 [0.36, 1.19]	0.16	
Mixed fiber	3	107/107	0	0.57 [0.40, 0.81]	0.002	
Unspecified	1	33/11	-	3.67 [0.53, 25.26]	0.19	
Soluble fiber	6	211/205	58	0.61 [0.39, 0.97]	0.03	Chi² = 3.81, df = 2 (p = 0.15), I² = 47%
Insoluble fiber	1	45/46	-	1.26 [0.69, 2.31]	0.46	
Mixed fiber	4	140/118	47	0.69 [0.33, 1.45]	0.33	
daily fiber dose < 20 g	5	175/149	33	0.96 [0.61, 1.50]	0.84	Chi² = 3.37, df = 2 (p = 0.19), I² = 40.7%
daily fiber dose ≥ 20 g	5	208/208	53	0.59 [0.37, 0.96]	0.04	
Unclear	1	13/12	-	0.50 [0.27, 0.93]	0.03	
Low risk of bias	0					
High risk of bias/ some concerns	11					
age < 50 years	6	213/211	59	0.68 [0.40, 1.15]	0.15	Chi² = 0.00, df = 1 (p = 0.98), I² = 0%
age ≥ 50 years	5	183/158	53	0.69 [0.43, 1.09]	0.11	
APACHE II < 17	3	155/134	51	0.64 [0.32, 1.28]	0.21	Chi² = 8.77, df = 2 (p = 0.01), I² = 77.2%
APACHE II ≥ 17	5	126/123	6	0.42 [0.25, 0.71]	0.001	
Unclear	3	115/112	0	1.00 [0.76, 1.32]	1.00	
Medical ICU	2	73/72	0	0.56 [0.40, 0.77]	0.0004	Chi² = 10.22, df = 3 (p = 0.02), I² = 70.6%
Surgical ICU	1	17/17	-	0.50 [0.18, 1.35]	0.17	
Mixed ICU	5	190/165	22	1.02 [0.73, 1.42]	0.93	
Unclear	3	116/115	0	0.37 [0.18, 0.74]	0.005	
intervention start ≤ 24h	3	90/87	60	0.63 [0.31, 1.29]	0.20	Chi² = 4.14, df = 3 (p = 0.25), I² = 27.6%
intervention start ≤ 48h	2	122/123	0	0.55 [0.39, 0.78]	0.0008	
intervention start ≥ 48h	1	33/11	-	3.67 [0.53, 25.26]	0.19	
Unclear	5	151/148	57	0.76 [0.43, 1.34]	0.34	
minimum duration of intervention < 6 days	4	127/126	18	0.95 [0.65, 1.39]	0.79	Chi² = 3.43, df = 2 (p = 0.18), I² = 41.6%
minimum duration of intervention ≥ 6 days	4	143/119	56	0.71 [0.41, 1.26]	0.24	
Unclear	3	126/124	48	0.35 [0.13, 0.98]	0.05	
co-intervention with immunonutrition	1	42/42	-	0.09 [0.01, 1.59]	0.10	Chi² = 1.97, df = 1 (p = 0.16), I² = 49.3%
fiber only	10	354/327	51	0.72 [0.52, 0.98]	0.04	
Industry funding	4	98/73	52	0.75 [0.43, 1.31]	0.31	Chi² = 0.35, df = 2 (p = 0.84), I² = 0%
Non-industry funding	2	97/96	64	0.70 [0.32, 1.49]	0.35	
Unclear funding	5	201/200	68	0.56 [0.26, 1.22]	0.14	
Standard formula in control group	10	354/327	51	0.72 [0.52, 0.98]	0.04	Chi² = 1.97, df = 1 (p = 0.16), I² = 49.3%
Non-standard formula in control group	1	42/42	51	0.09 [0.01, 1.59]	0.10	

Table S12: Calculation of daily fiber doses

Reference No	Author, year	Daily fiber dose	Variables	Calculation*
[38]	Hart, 1988	7 g/d	-	Fiber/d reported
[39]	Dobb, 1990	21 – 42 g/d	Fiber: 21g/l Feed volumes from day 3: mean volume of 1000-2000 ml	$Daily\ fiber\ dose1 = 1000\ ml\ \times\ (21g/1000\ ml) =\ 21\ g$ $Daily\ fiber\ dose2 = 2000\ ml\ \times\ (21g/1000\ ml) =\ 42\ g$
[47]	Celaya, 1992	NI	NI	-
[35]	Caparrós, 2000	11.7 g/d	Fiber: 13.5g/1500ml Caloric density: 1.25kcal/ml Administered caloric intake day 3: 1625 (1137 – 1828) kcal	$Daily\ fiber\ dose = \frac{1625\ kcal}{1.25\ kcal/ml} \times 13.5\ g/1500ml = 11.7\ g$
[41]	Schultz, 2000	15.8 – 17.3 g/d	-	Fiber/d reported
[43]	Spapen, 2001	NI	NI	-
[40]	Rushdi, 2004	22-24 g/d	-	Fiber/d reported
[37]	Palmese, 2006	10.6 g/d	-	Fiber/d reported
[49]	Karakan, 2007	24 g/d	-	Fiber/d reported
[46]	Spindler-Vesel, 2007	20.68 g/d	Fiber: 22 g/l Total feed volumes day 2 to 4: 2820 (2300 – 3100) ml	$Daily\ fiber\ dose = \frac{2820\ ml\ \times\ (22g/1000\ ml)}{3\ days} =\ 20.68\ g$
[45]	Chitta-watanarat, 2010	22.65 g/d	Fiber: 15.1 g/l Caloric density: 1000 kcal/l Mean caloric intake day 6: 1500 kcal	$Daily\ fiber\ dose = \frac{1500\ kcal}{1000\ kcal/l} \times 15.1\ g/l = 22.65\ g$
[52]	Zavertailo, 2010	NI	NI	-
[53]	Aytünür	18 g/d	Fiber: 10.6 g/l Caloric density: 1.1 kcal/l Max. calories per day: 1867 ± 120.18 ml	$Daily\ fiber\ dose = \frac{1867\ kcal}{1.1\ kcal/ml} \times 10.6\ g/l = 18\ g$
[51]	Wang, 2014	NI	NI	-
[36]	Kamarul Zaman, 2016	14.8 g/d	-	Fiber/d reported
[44]	Yagmurdur, 2016	28 g/d	-	Fiber/d reported
[54]	Xi, 2017	24 g/d	-	Fiber/d reported
[50]	Fazilaty, 2018	3 g/d	-	Fiber/d reported
[42]	Freedberg, 2020	11 g/d	-	Fiber/d reported
[48]	Chen, 2021	20 g/d	-	Fiber/d reported
Median value		**20 g/d**		

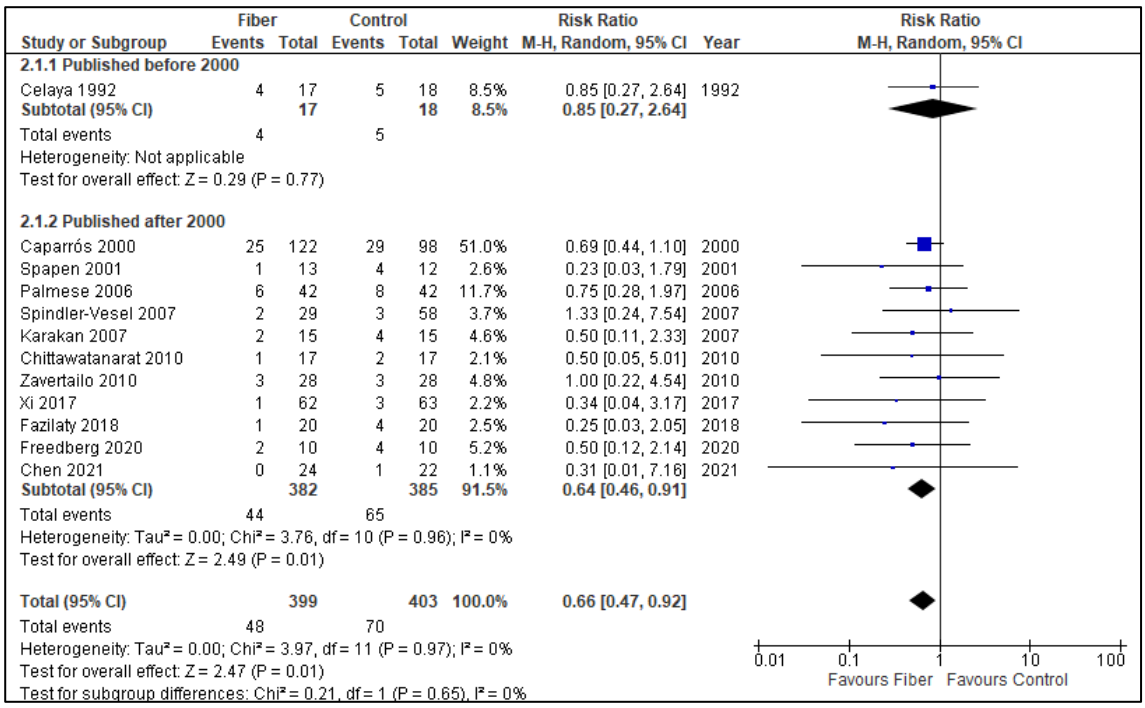
In studies reporting the evolution of feed volume or caloric intake over the study period, daily fiber dose calculations for subgroup analysis were based on maximum observed values. We associated maximum values with the achievement of caloric goals, thereby ensuring that the calculated fiber doses are valid for most of the study period.

If median (IQR) or mean + SD of caloric intake/feed volumes were given, median or mean were used for the calculation.

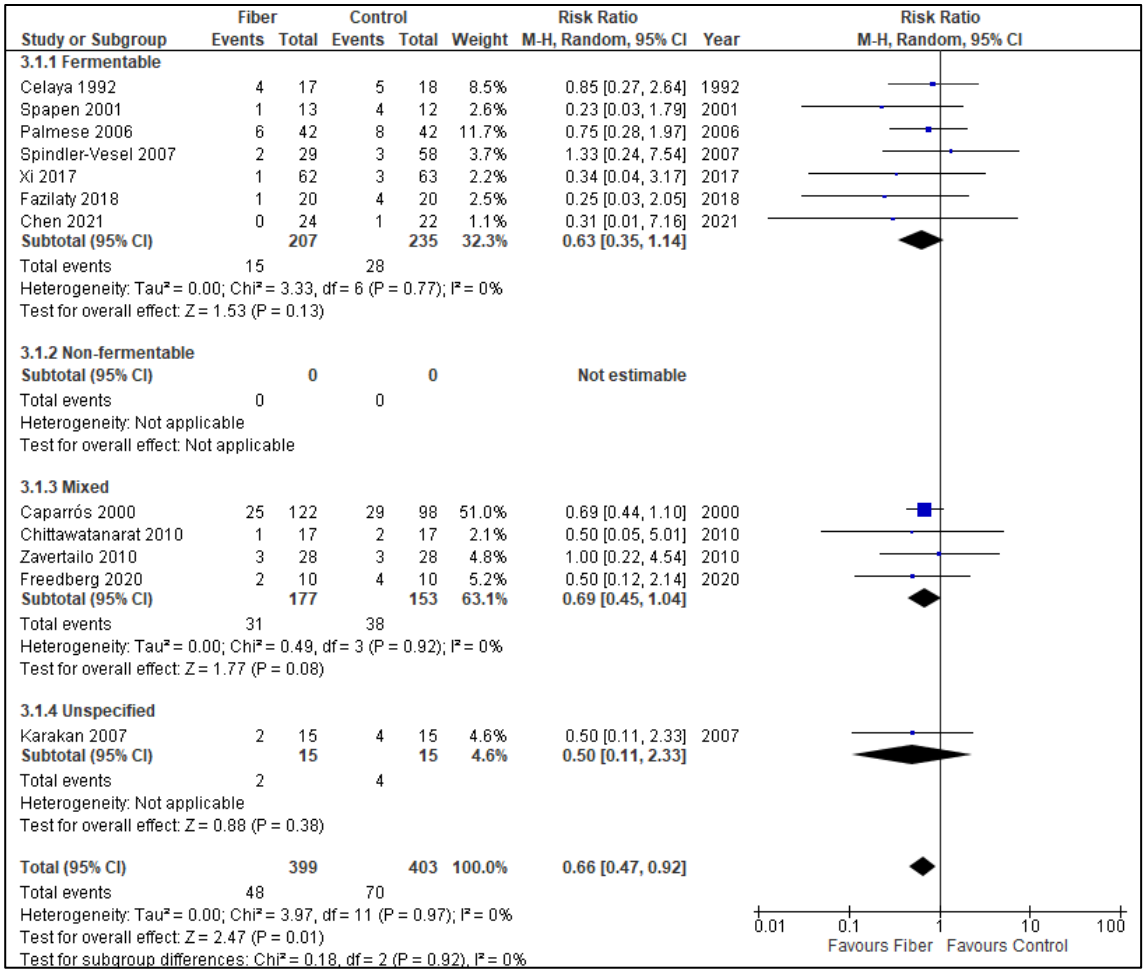
When a range of daily fiber dose was reported, both values were used for the calculation of the median value of all fiber doses.

Figure S2: Overall mortality (subgroup analyses)

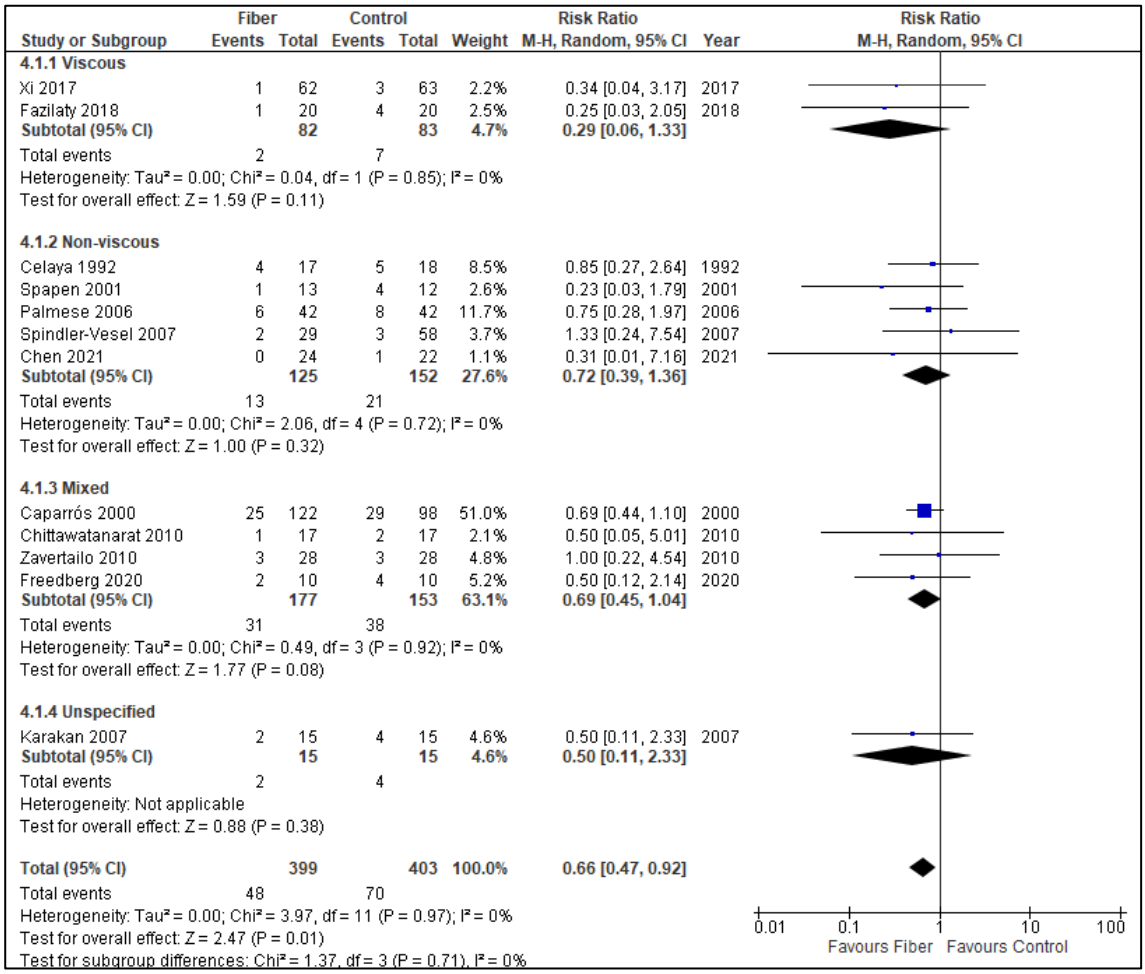
2a) Publication date



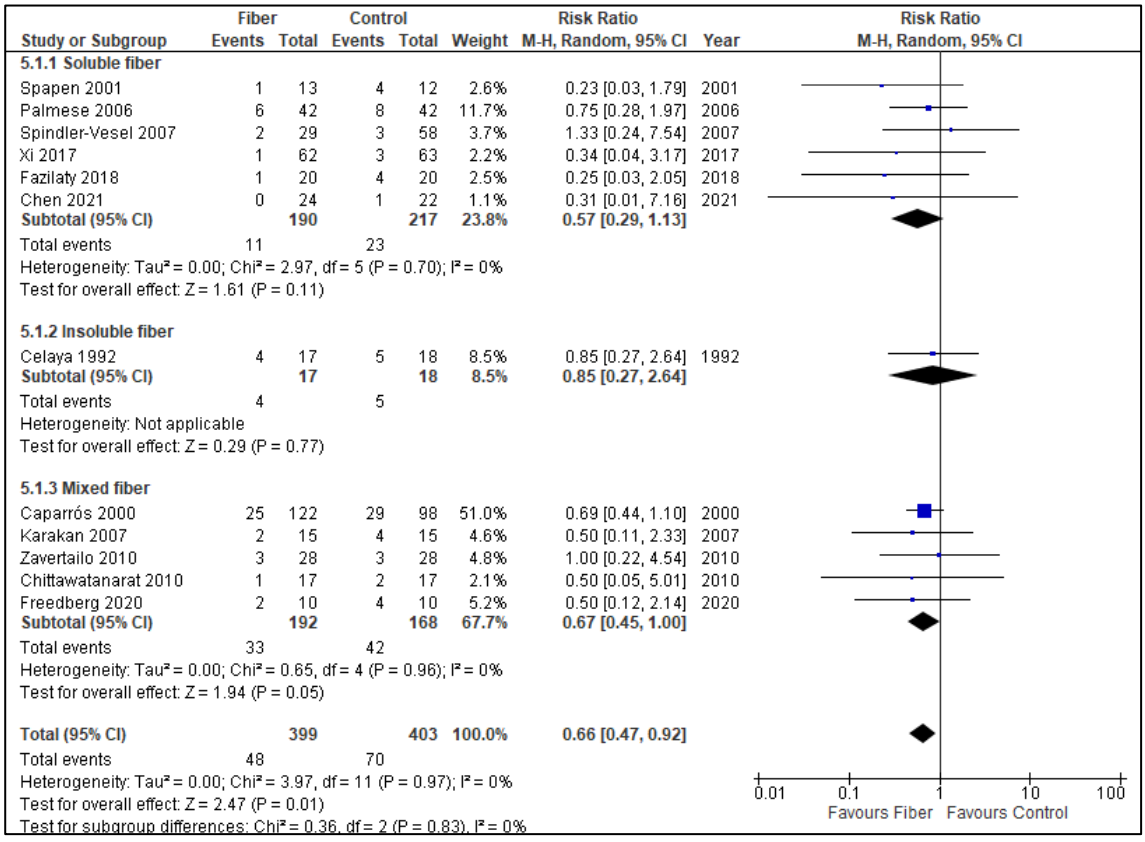
2b) Fermentability



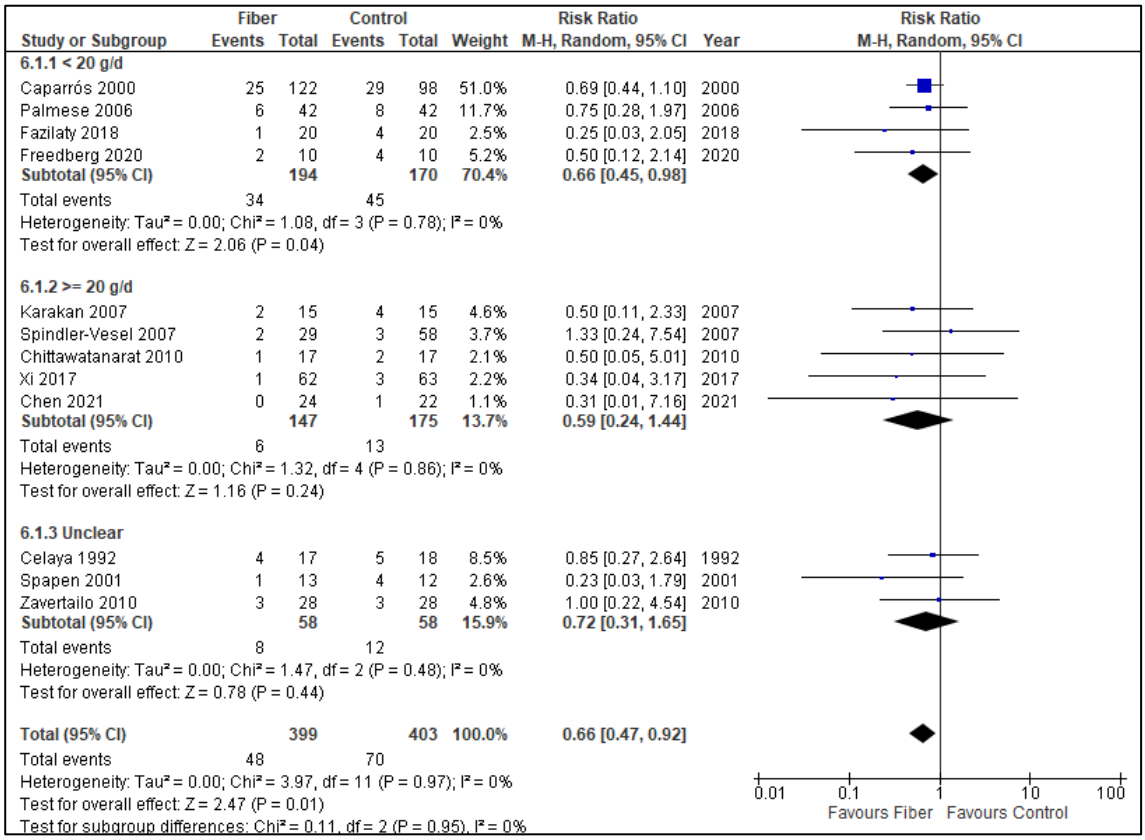
2c) Viscosity



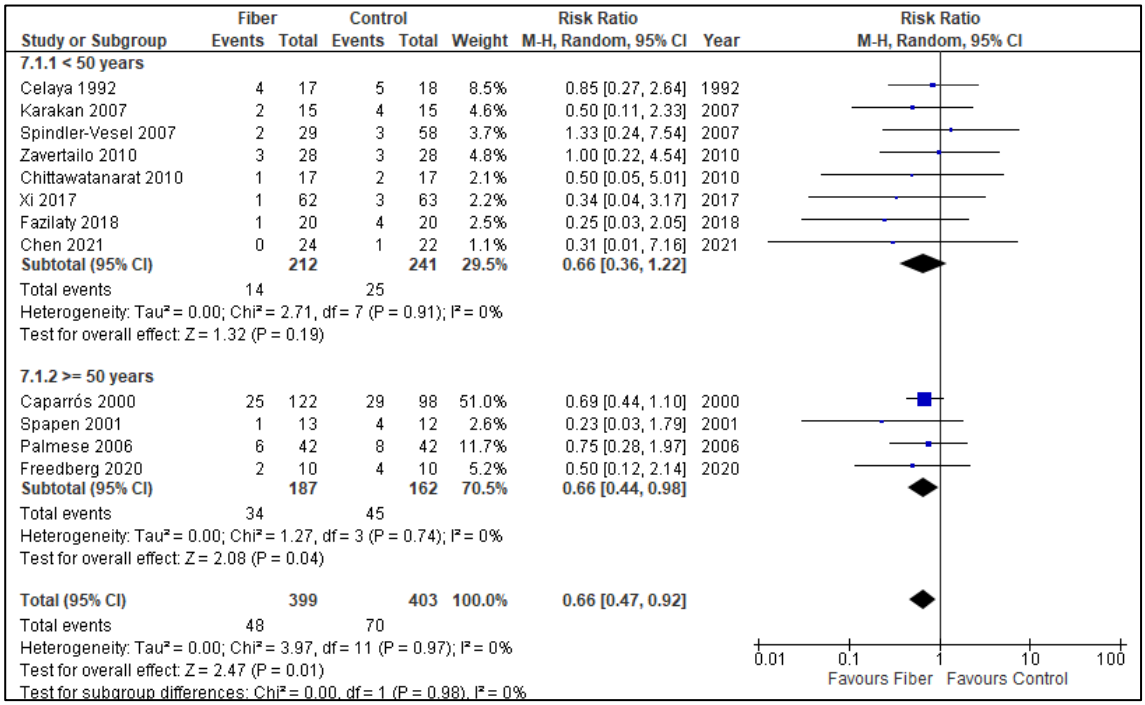
2d) Solubility



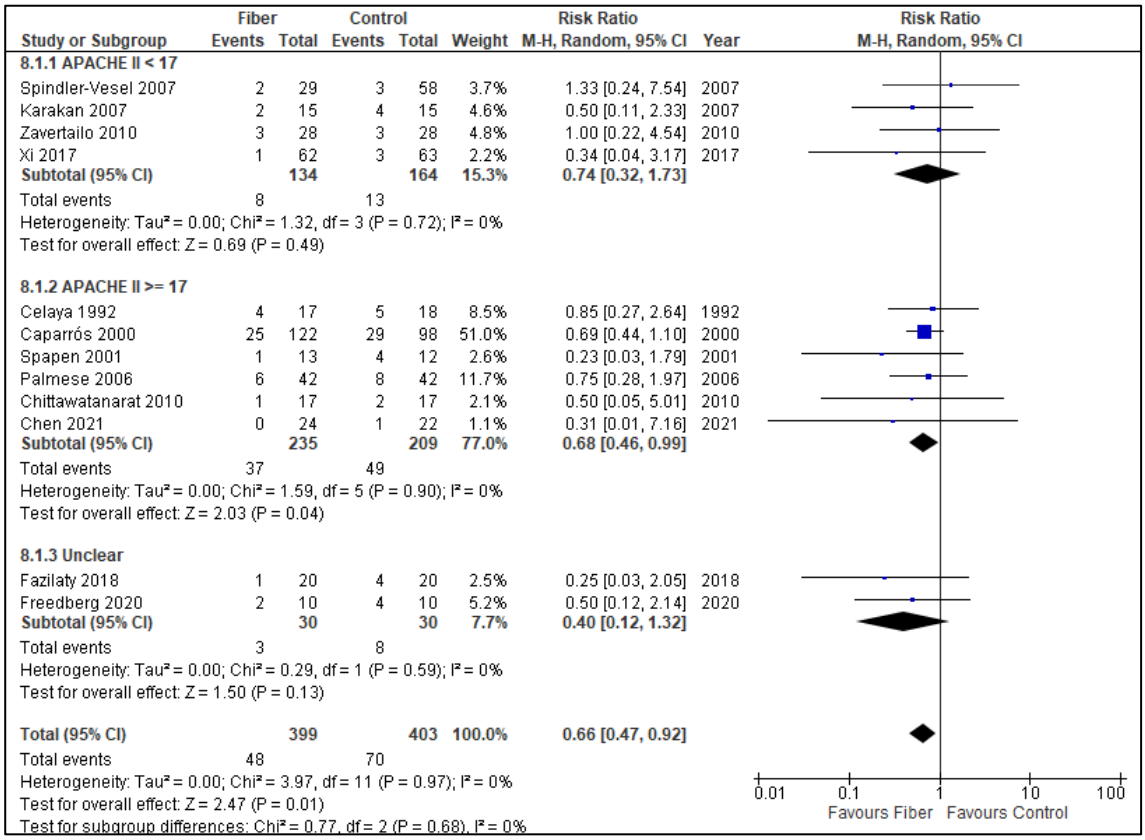
2e) Daily fiber dose



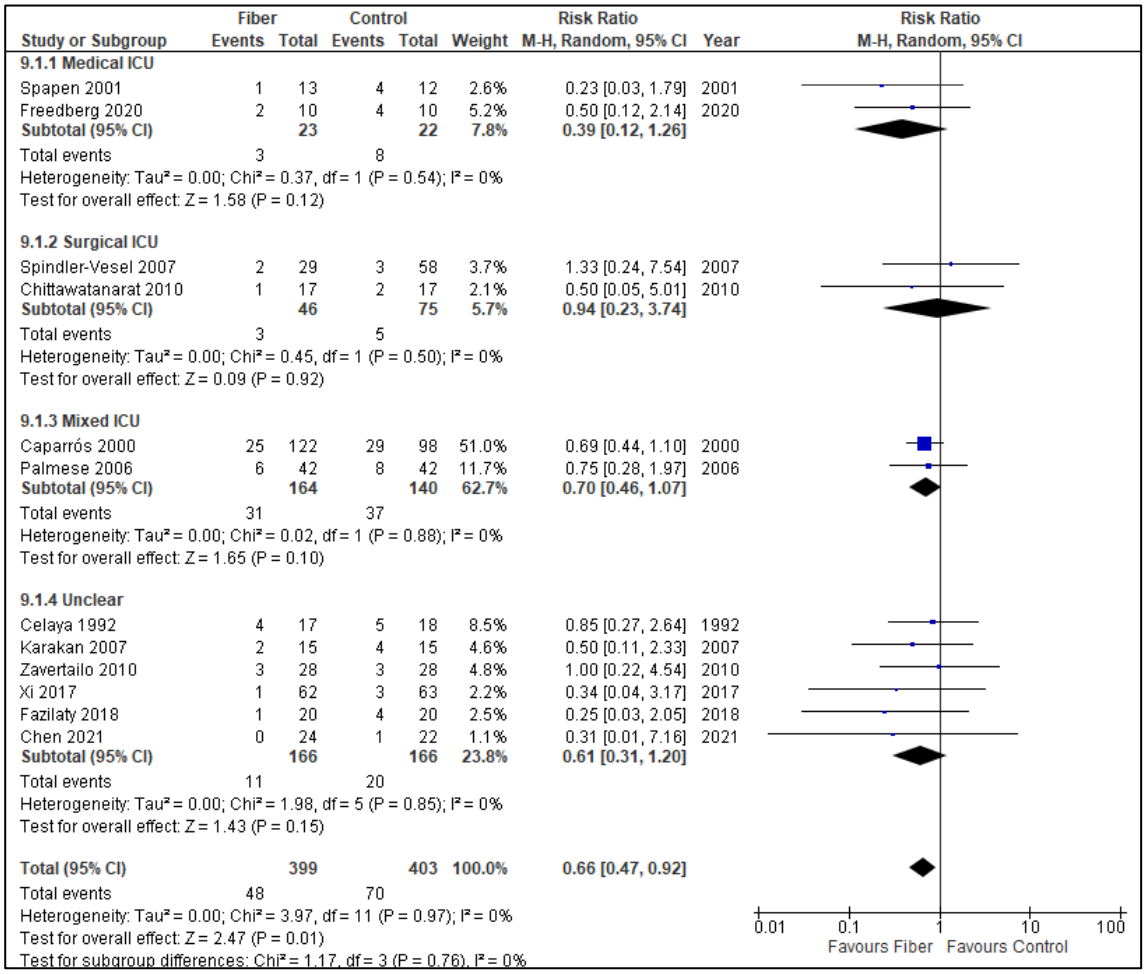
2f) Age



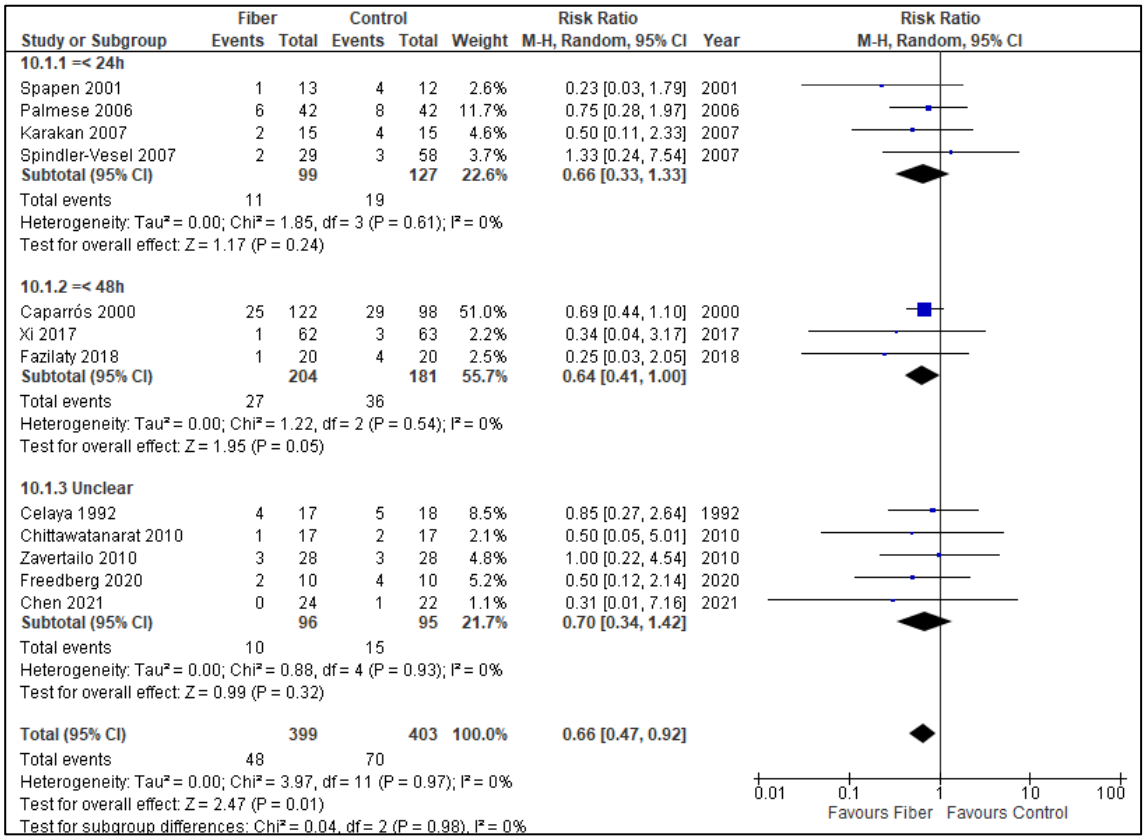
2g) Disease severity



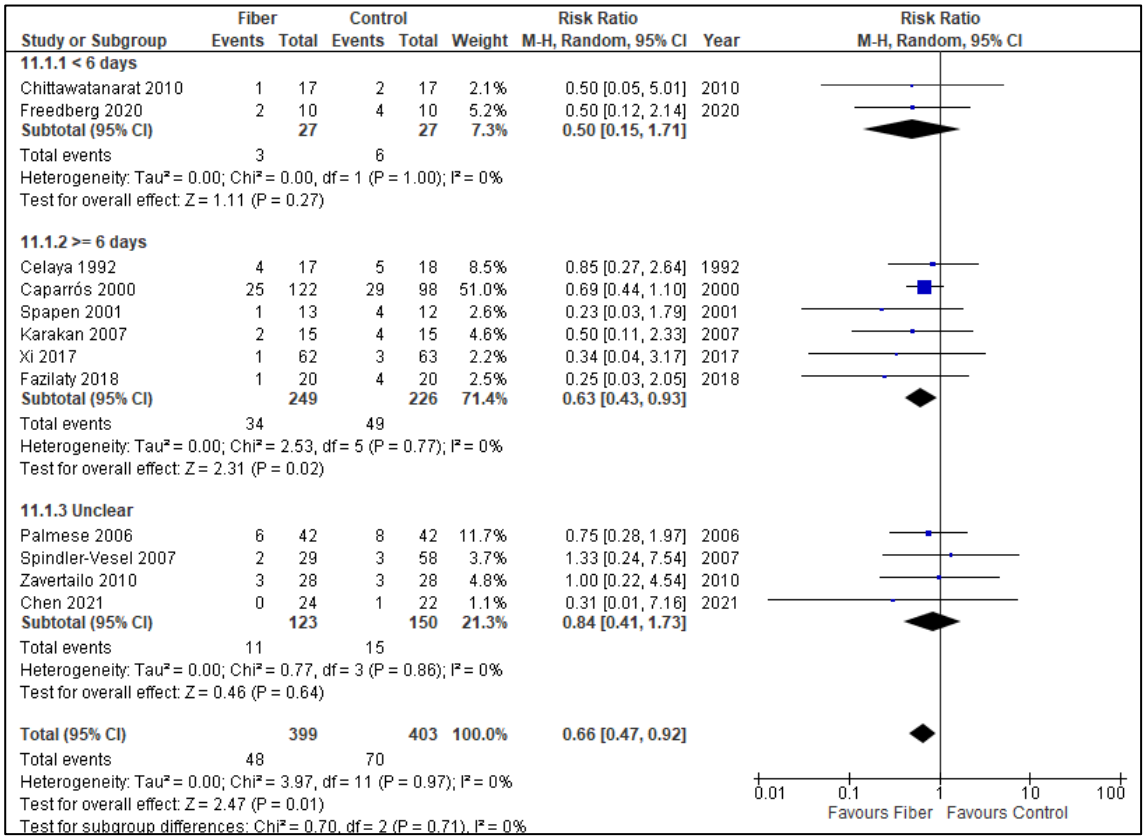
2h) ICU admission type



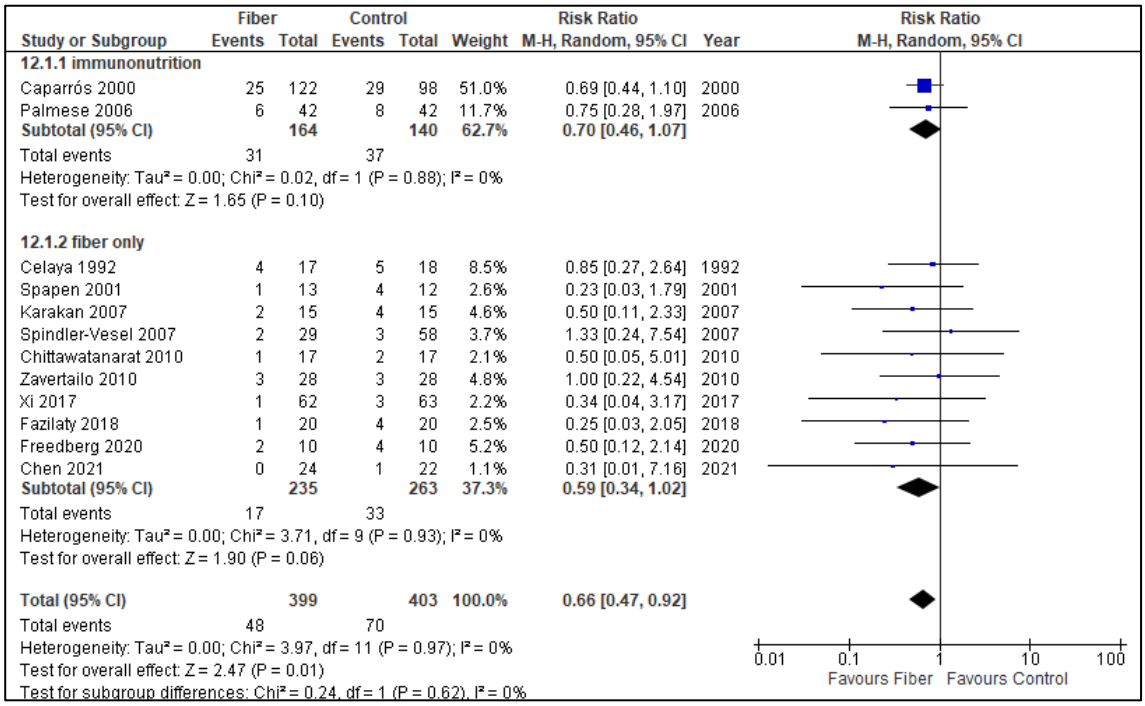
2i) Intervention start



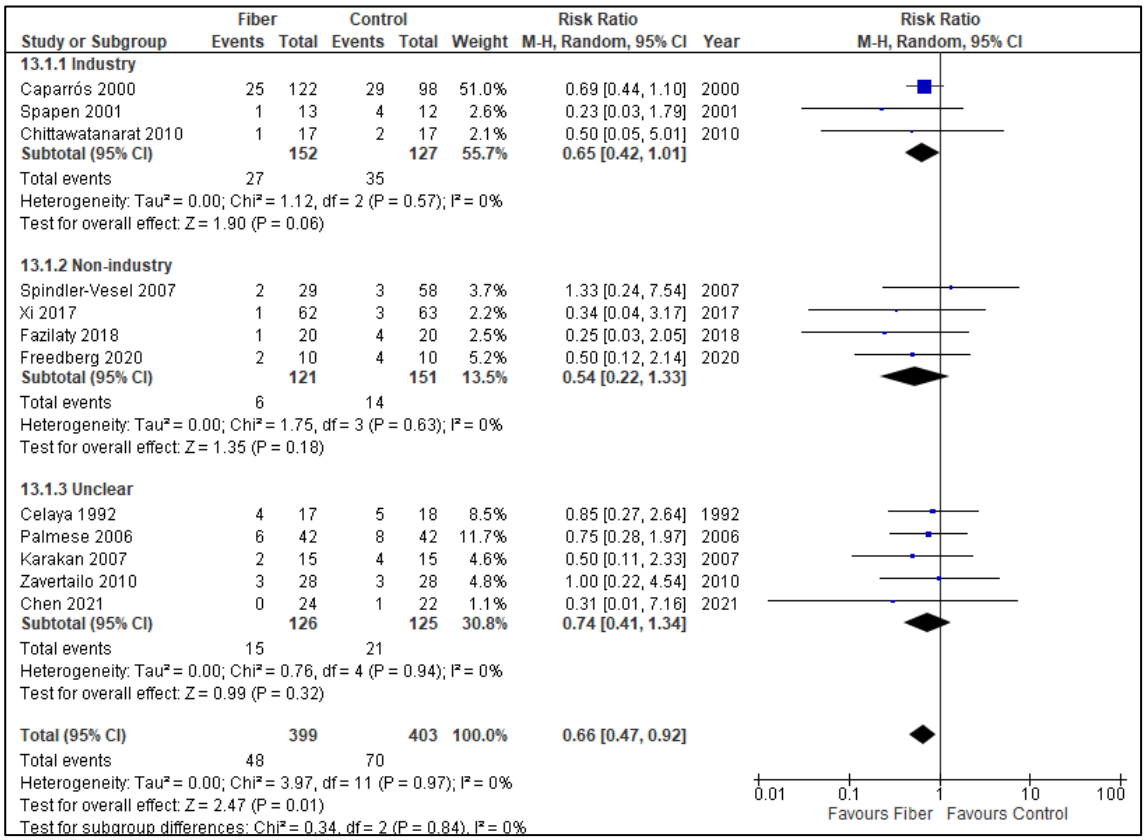
2j) Minimum duration of intervention



2k) Co-intervention with immunonutrition



2l) Funding source



2m) Type of control group

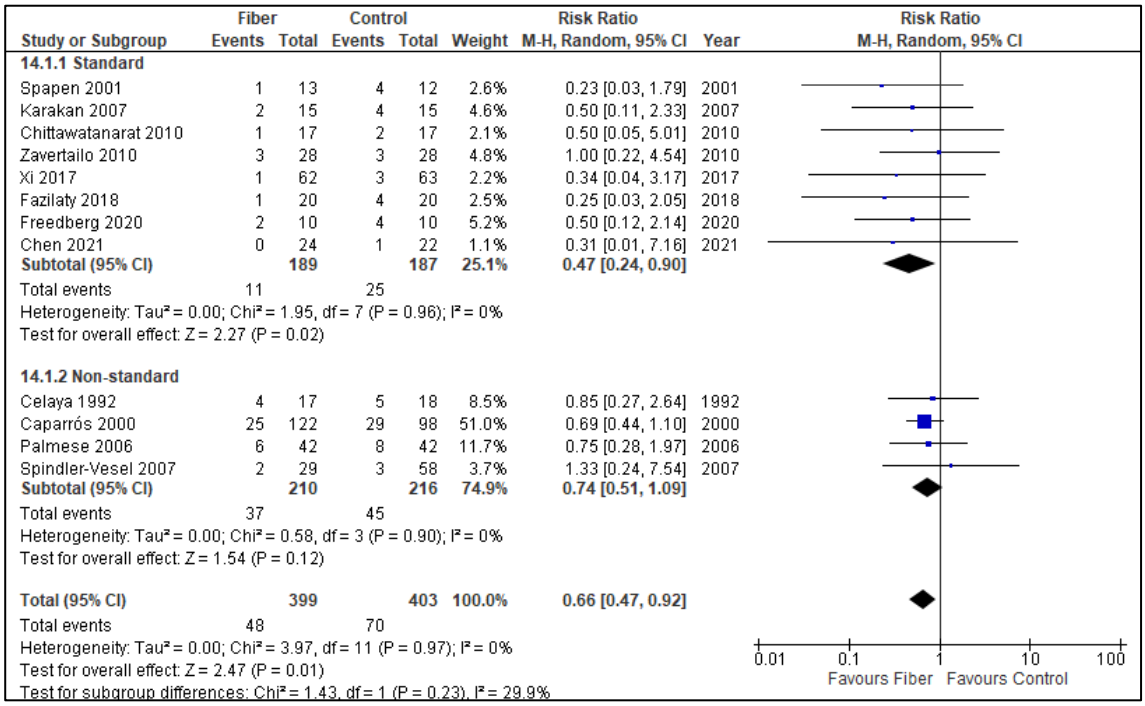
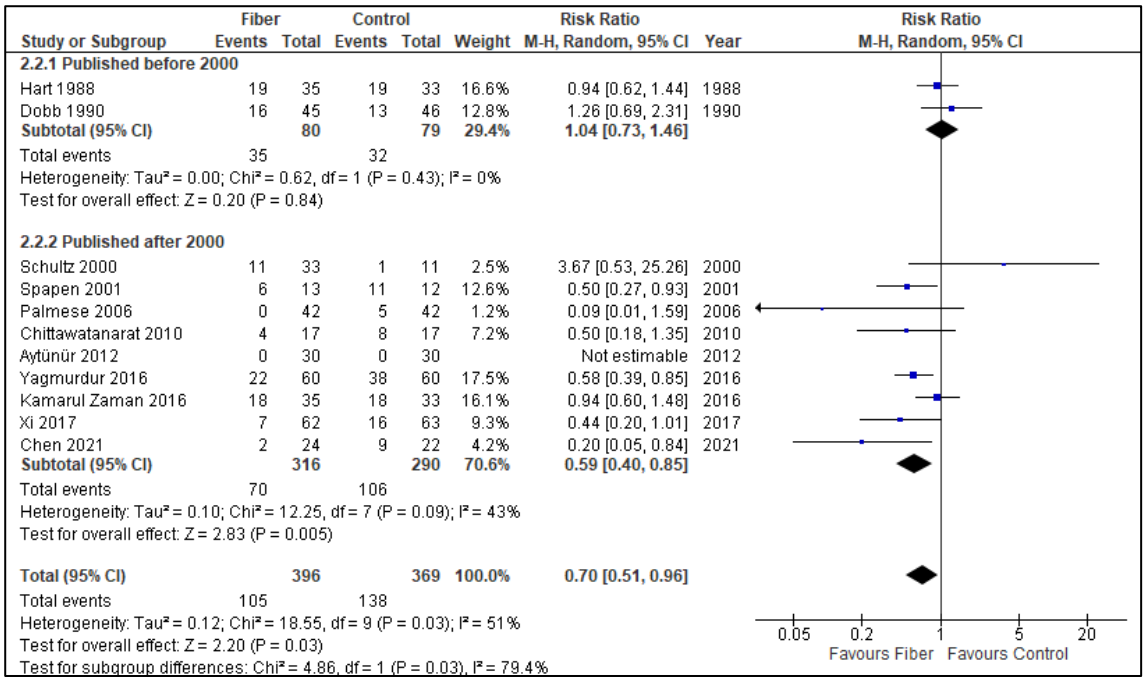
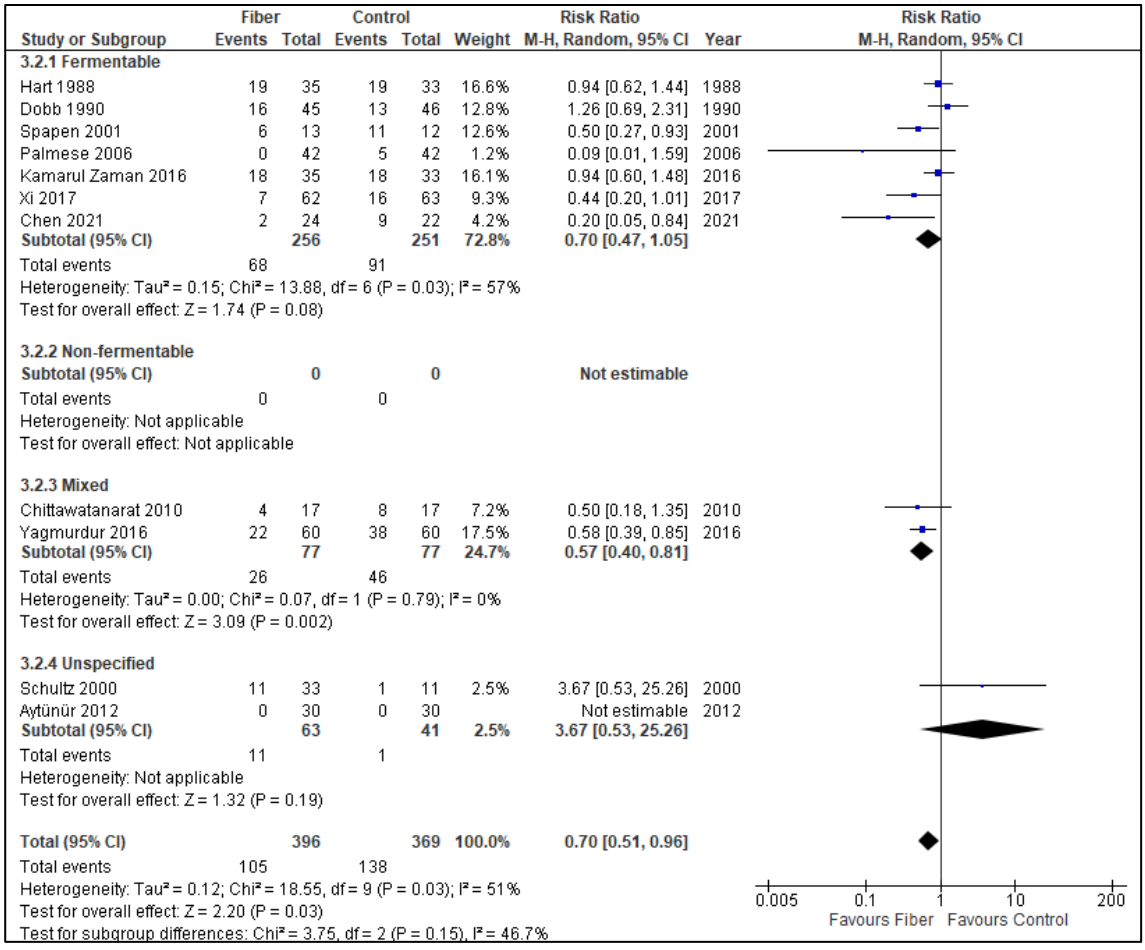


Figure S3: Diarrhea incidence (subgroup analyses)

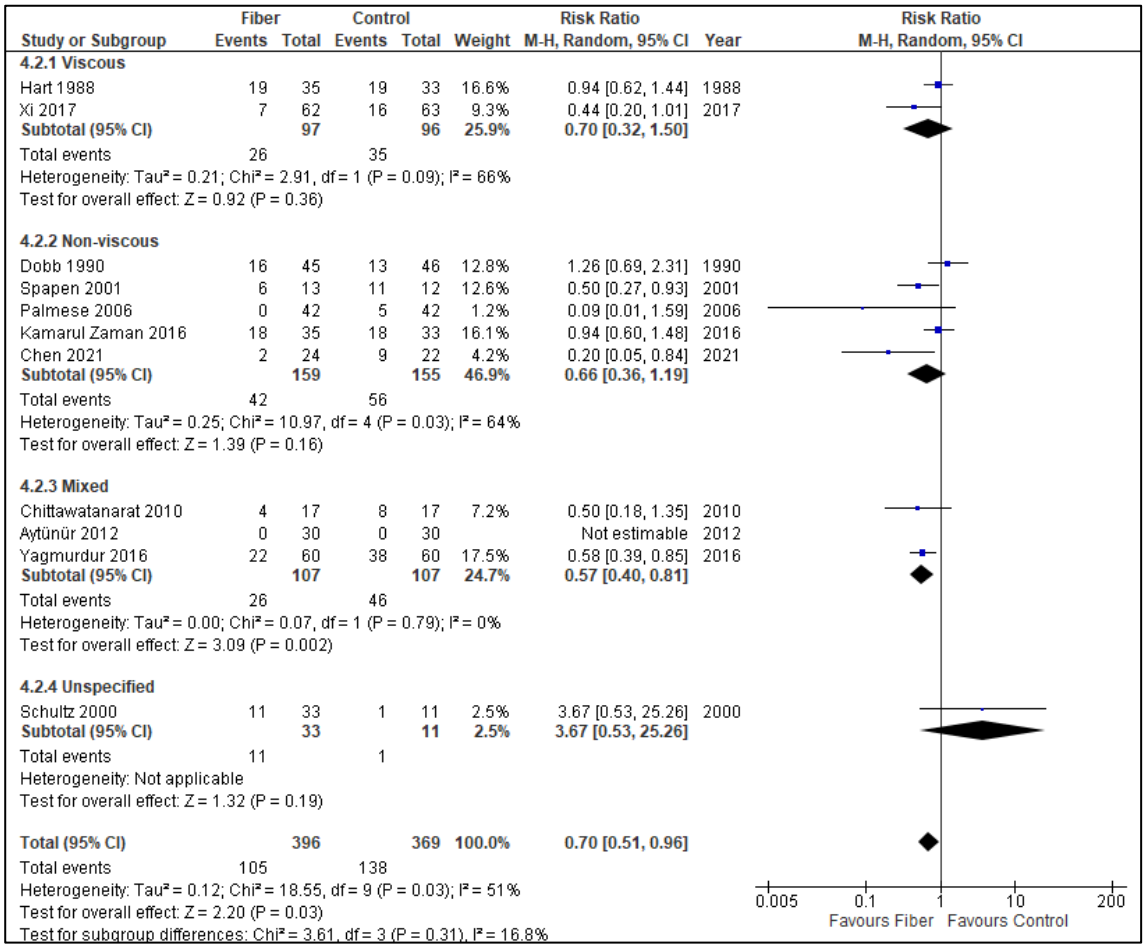
3a) Publication date



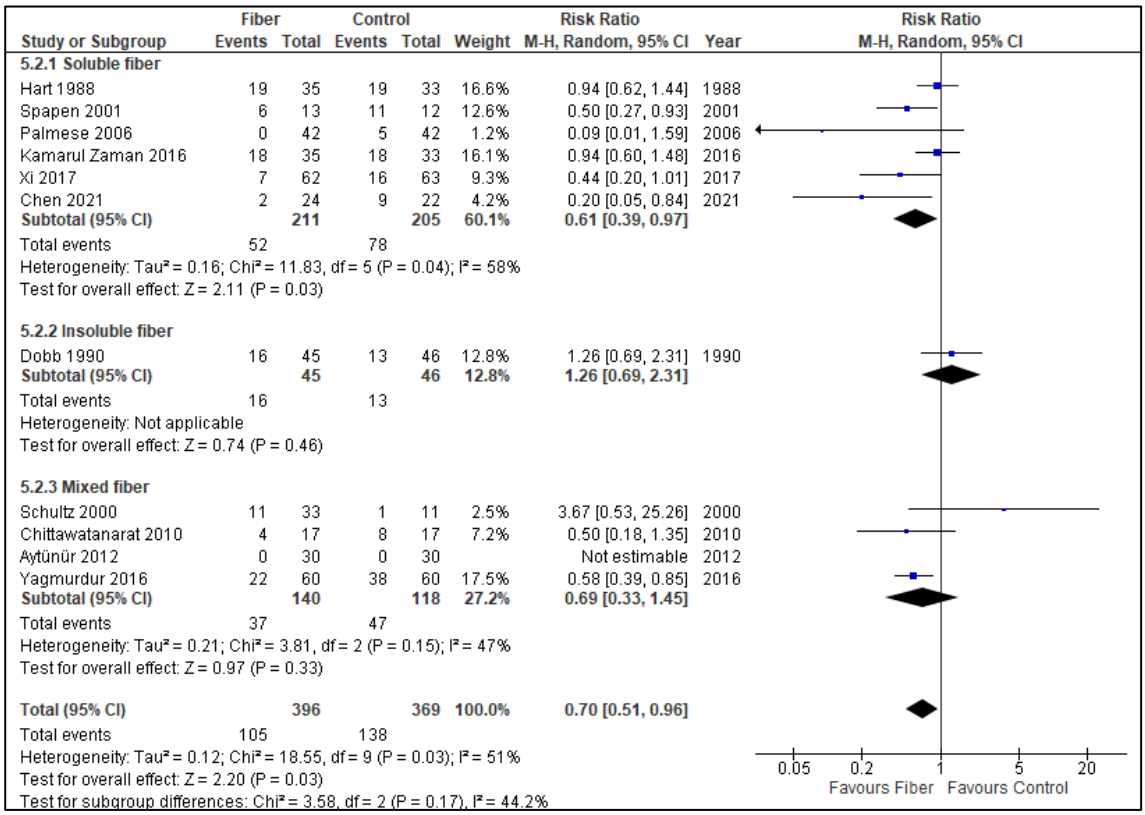
3b) Fermentability



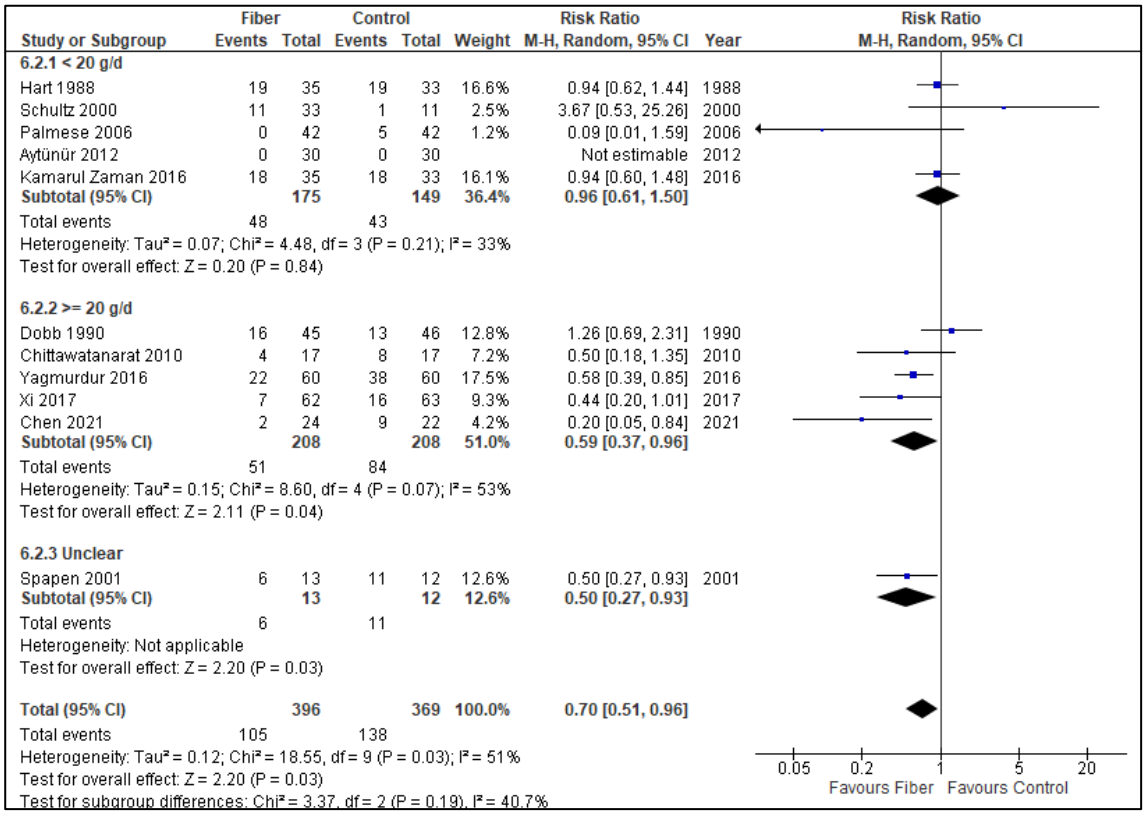
3c) Viscosity



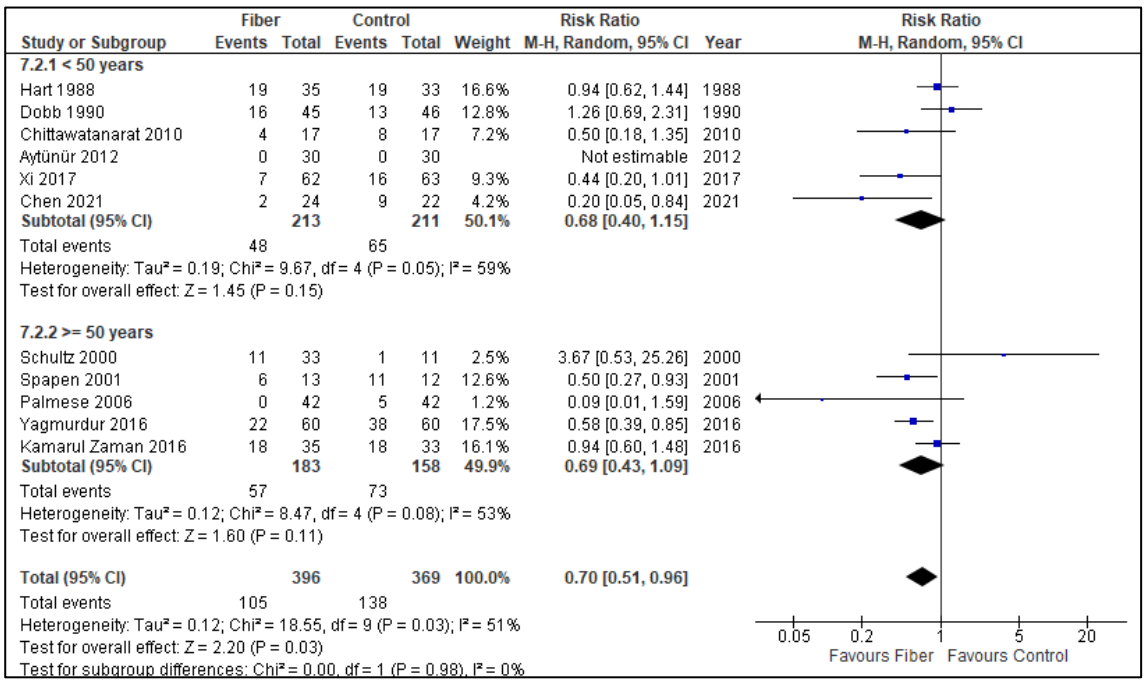
3d) Solubility



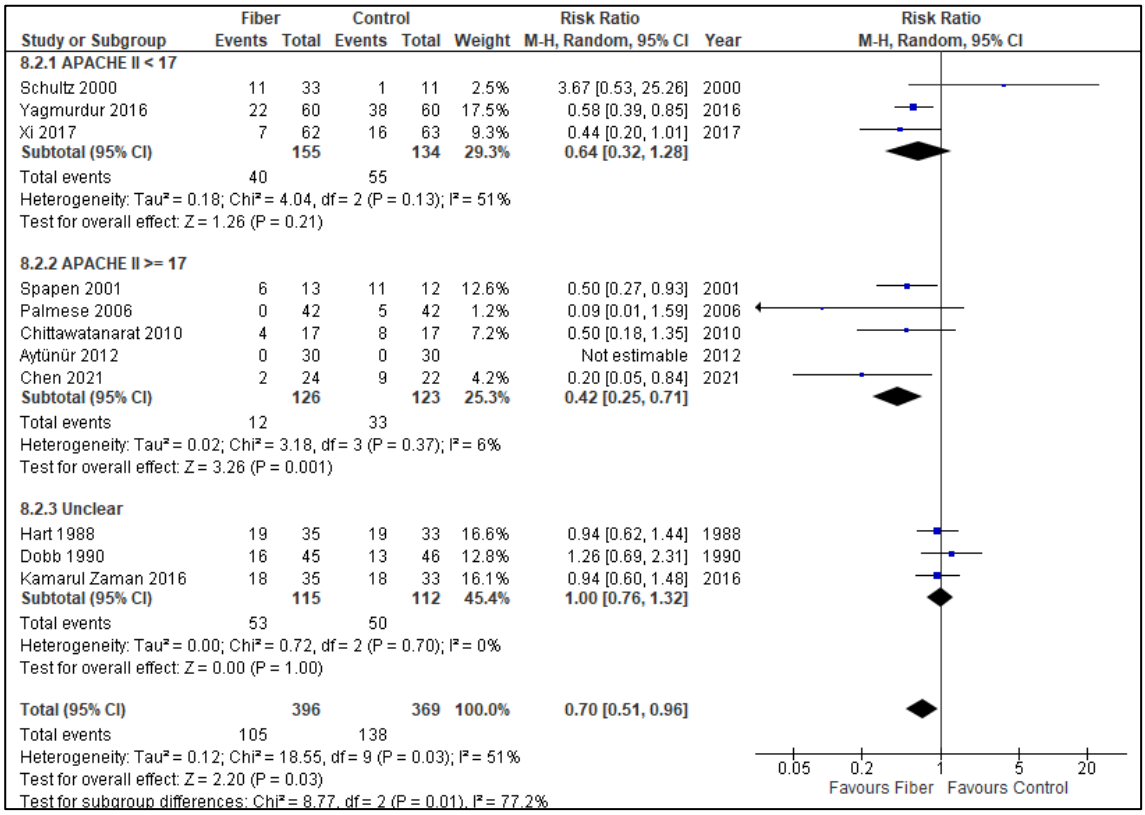
3e) Daily fiber dose



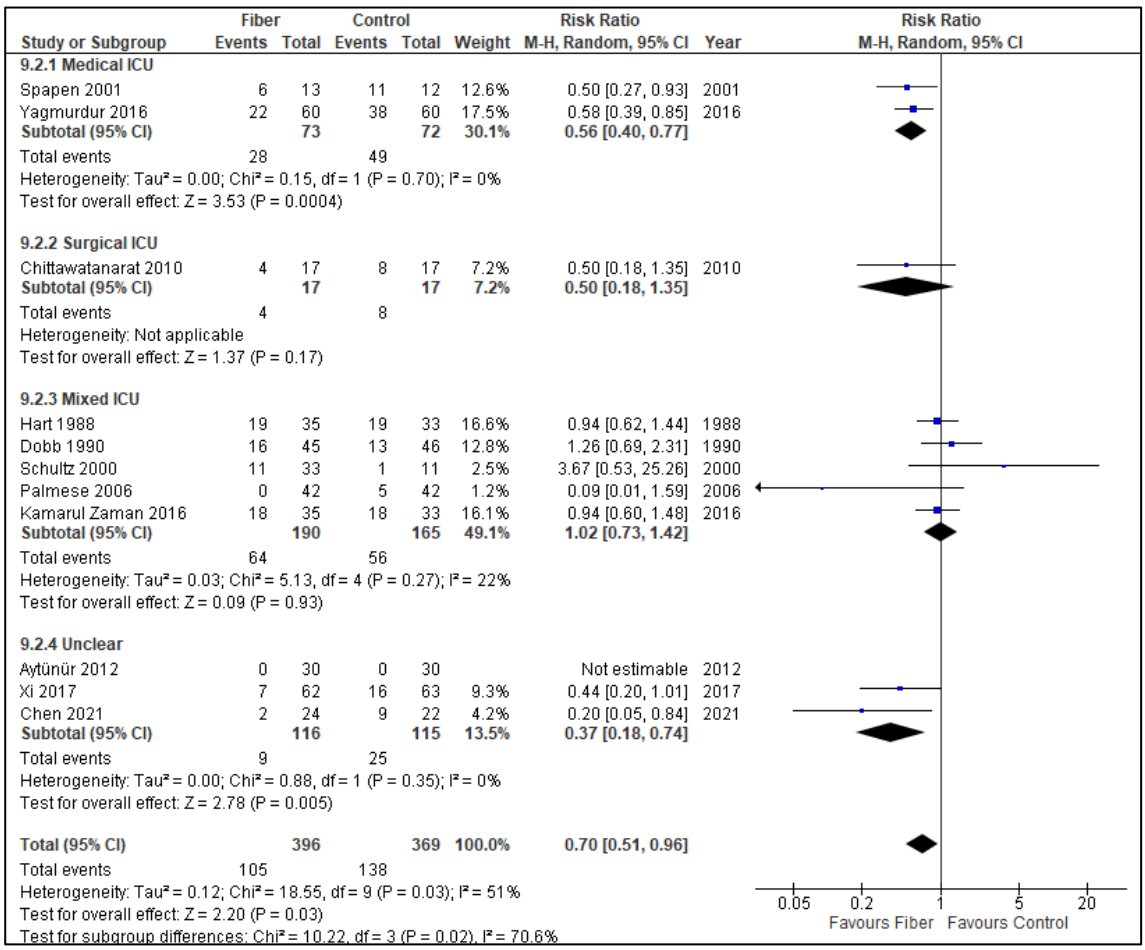
3f) Age



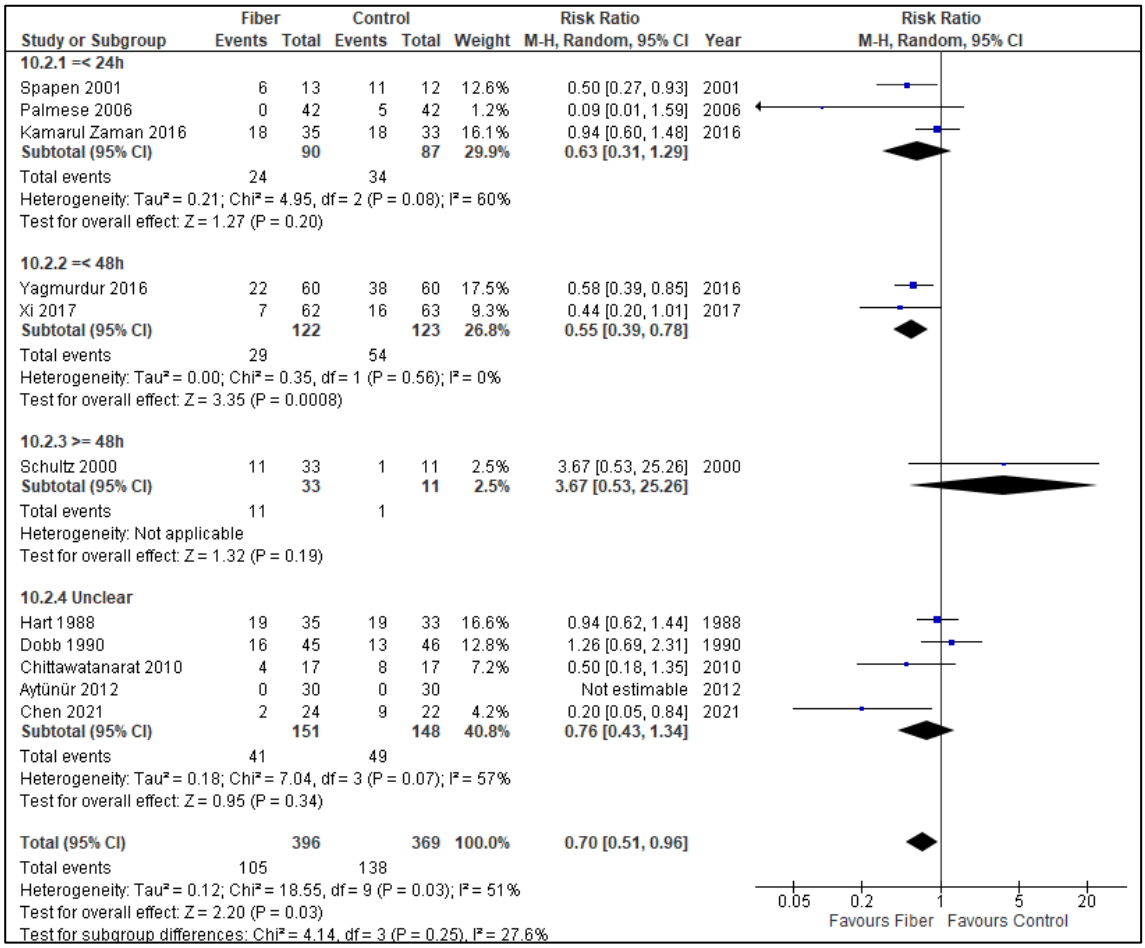
3g) Disease severity



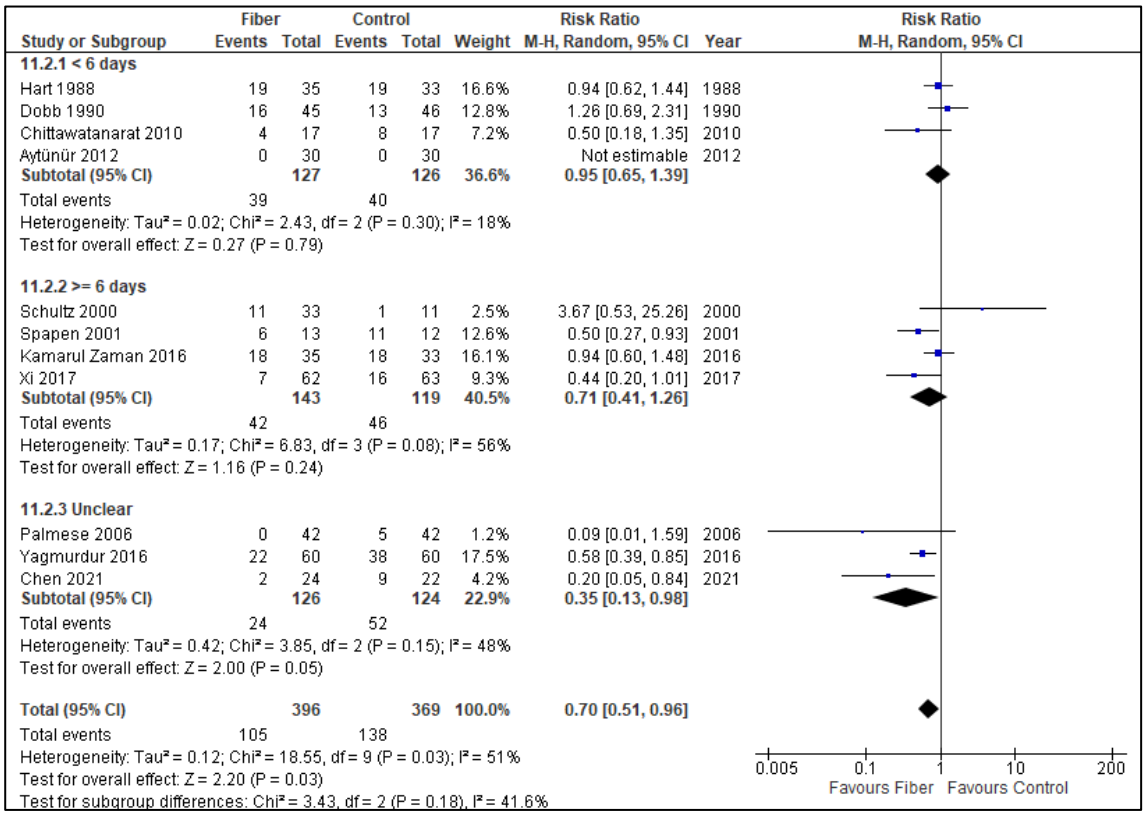
3h) ICU admission type



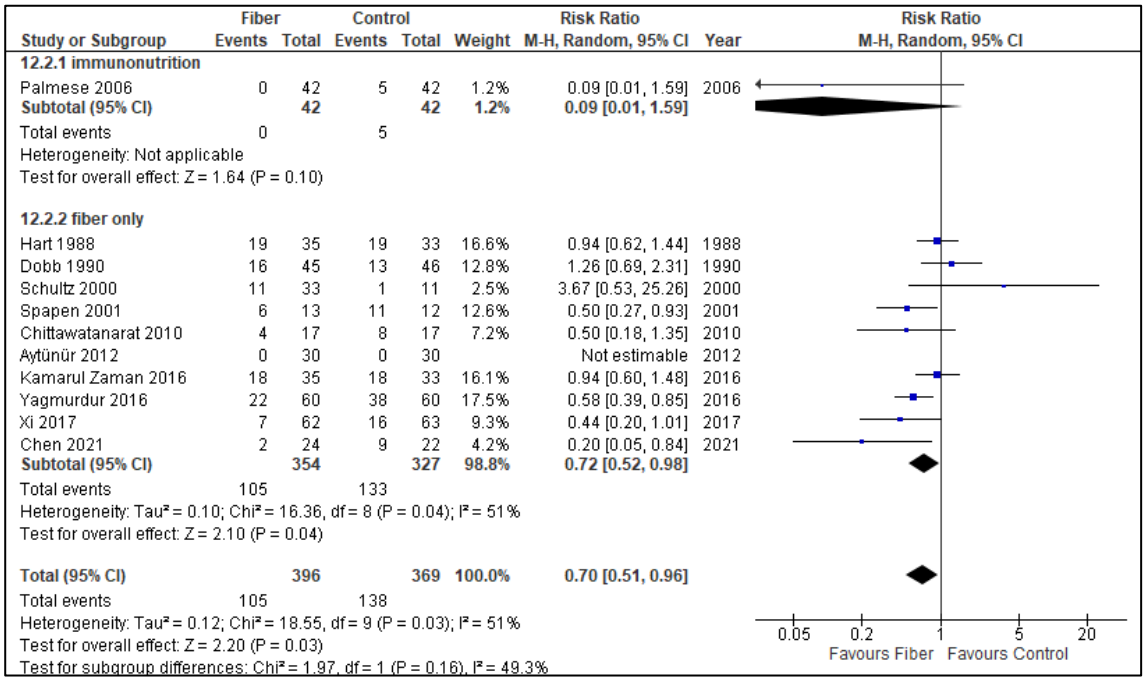
3i) Intervention start



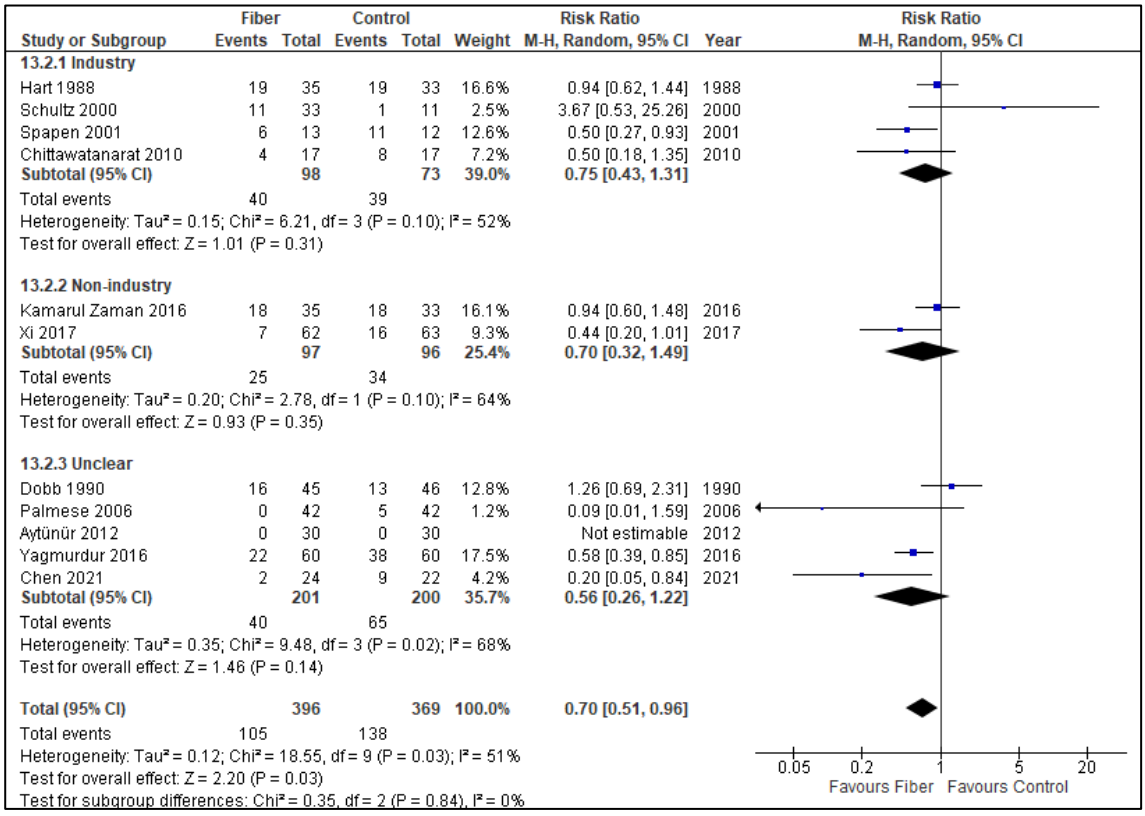
3j) Minimum duration of intervention



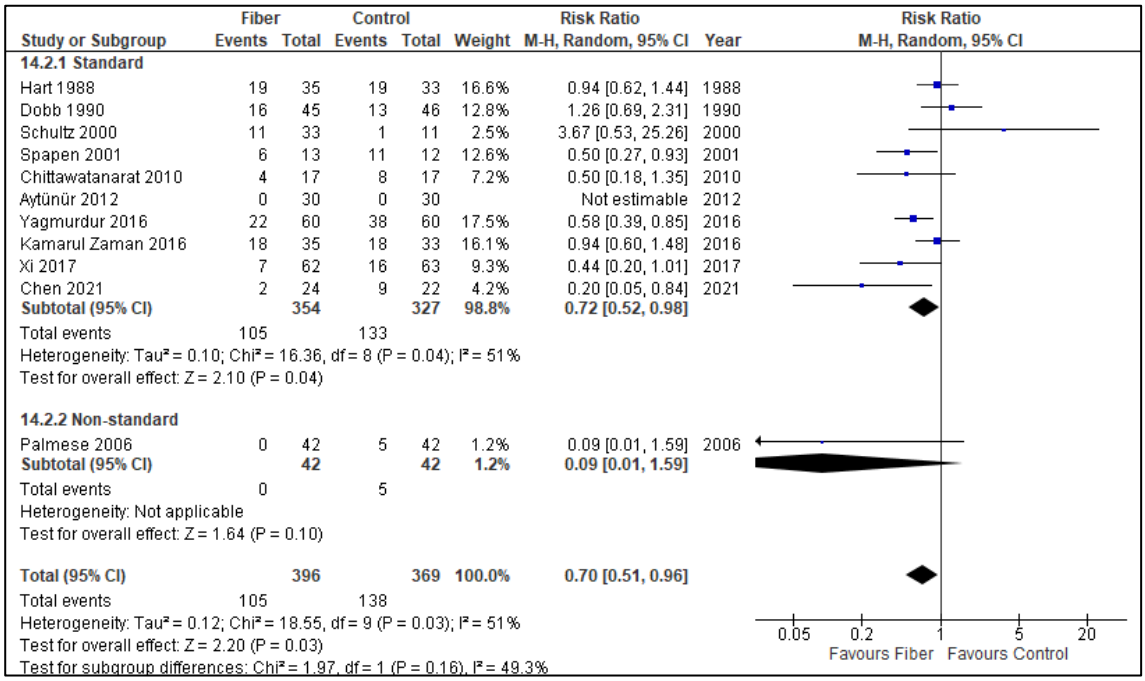
3k) Co-intervention with immunonutrition



3l) Funding source



3m) Type of control group



PART 3B: Overall meta-analyses

Figure S4: Diarrhea score

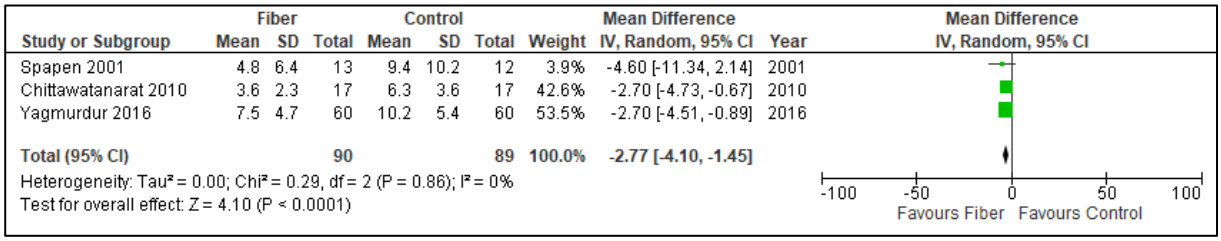
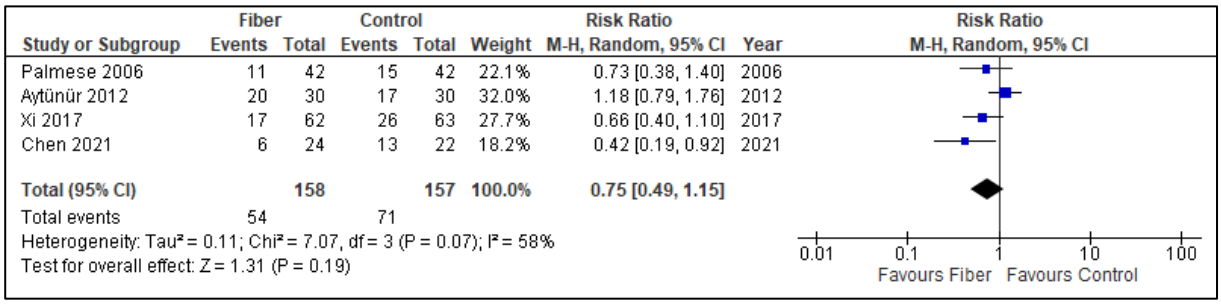
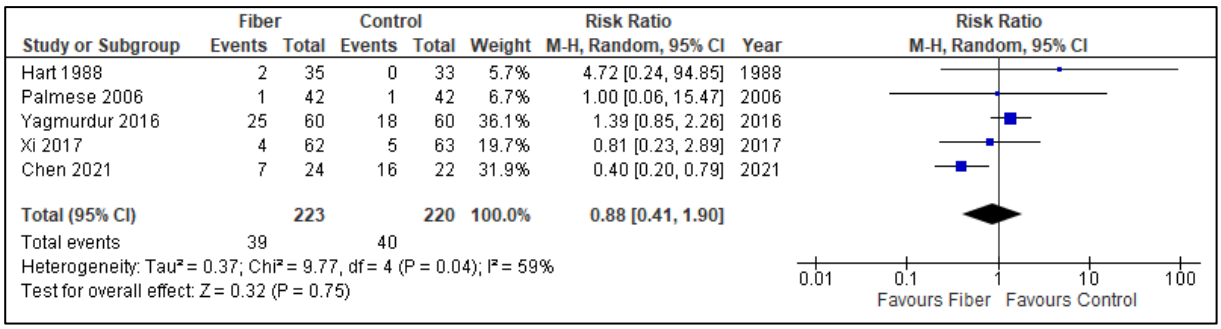


Figure S5: Other GI complications

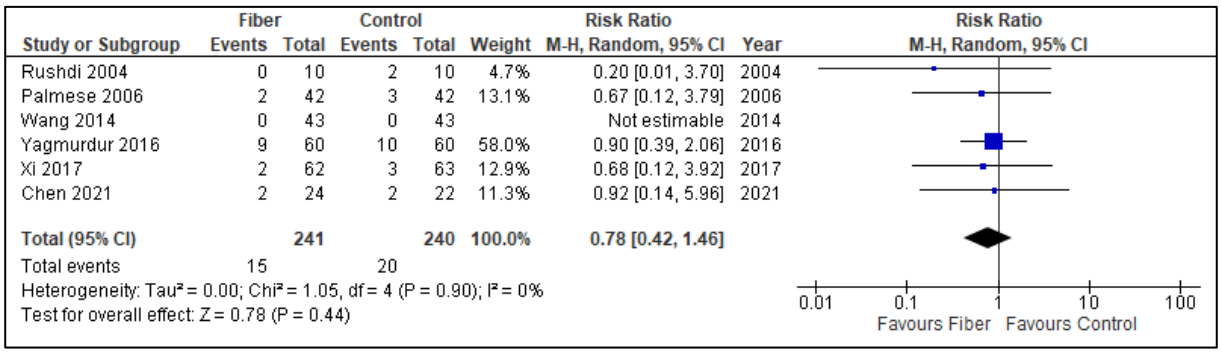
5a) Patients with at least one GI complication



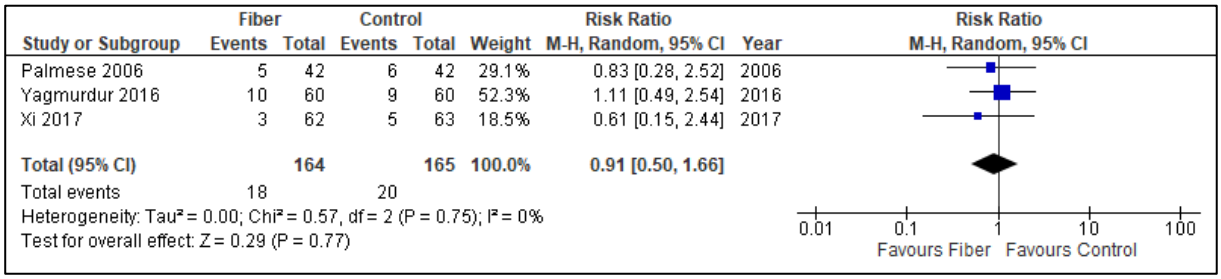
5b) Abdominal distension



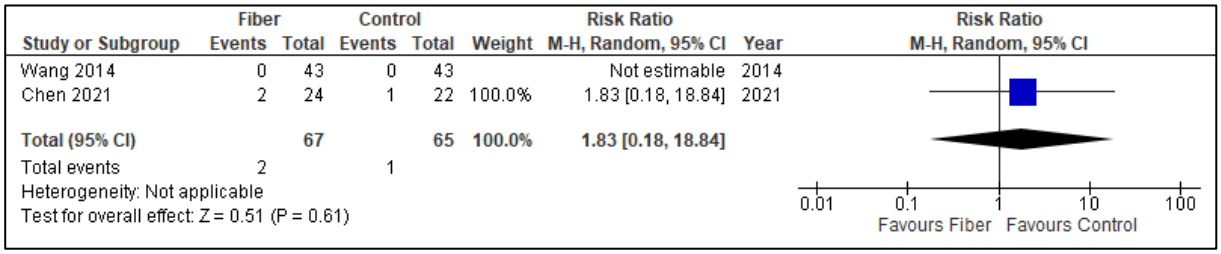
5c) Vomiting



5d) Regurgitation



5e) GI bleeding



5f) Constipation

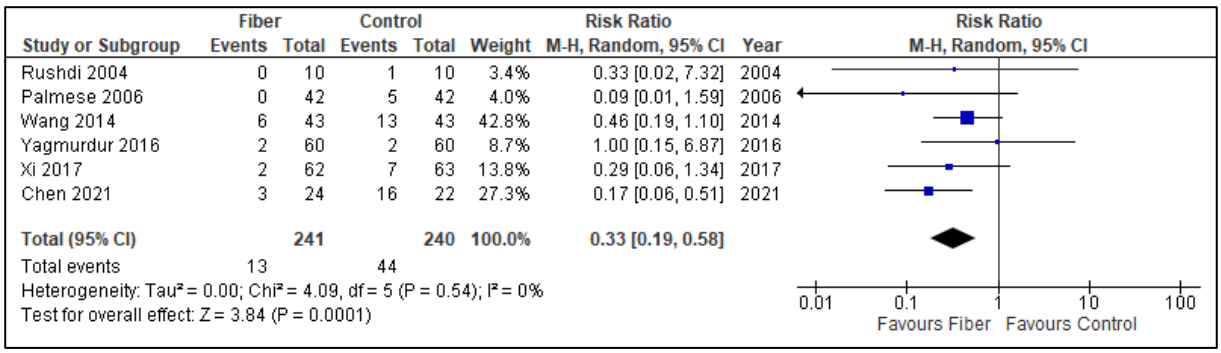
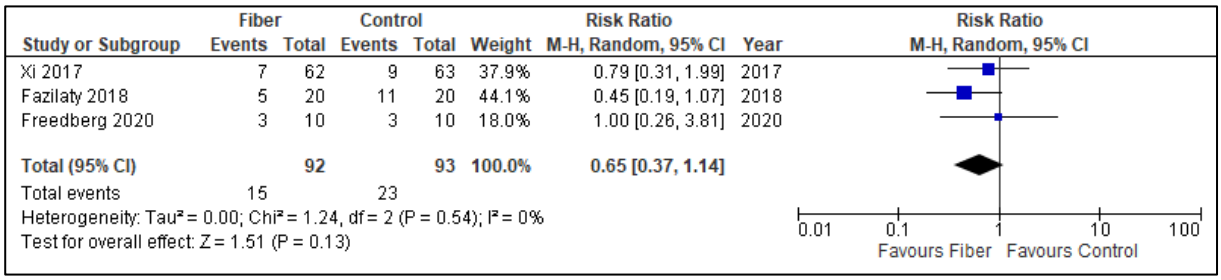
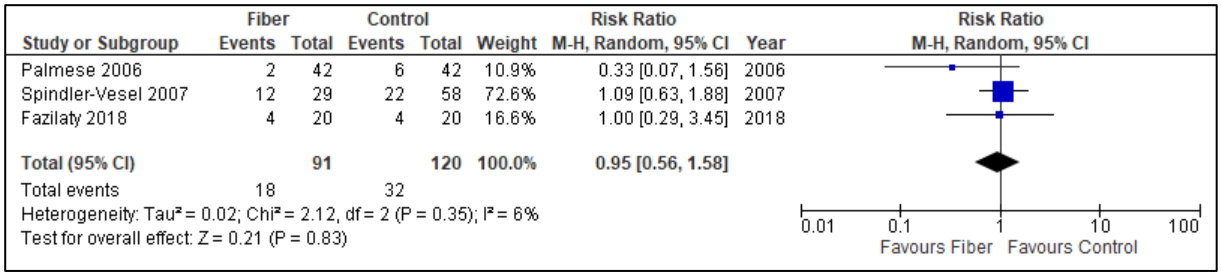


Figure S6: Infectious complications

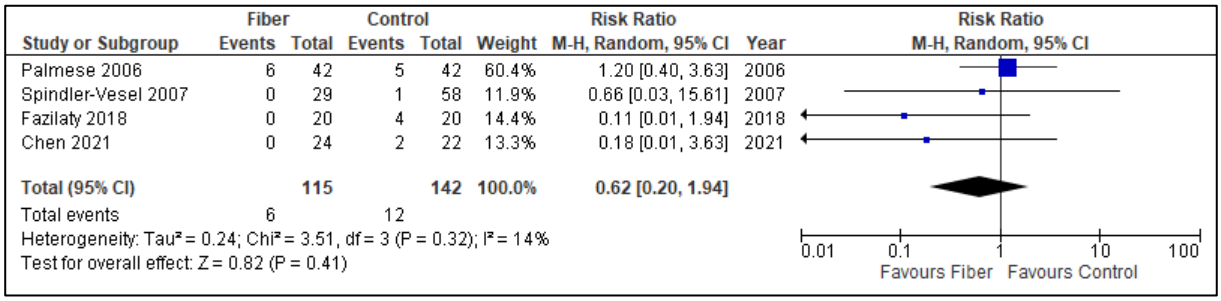
6a) Patients with at least 1 infectious complication



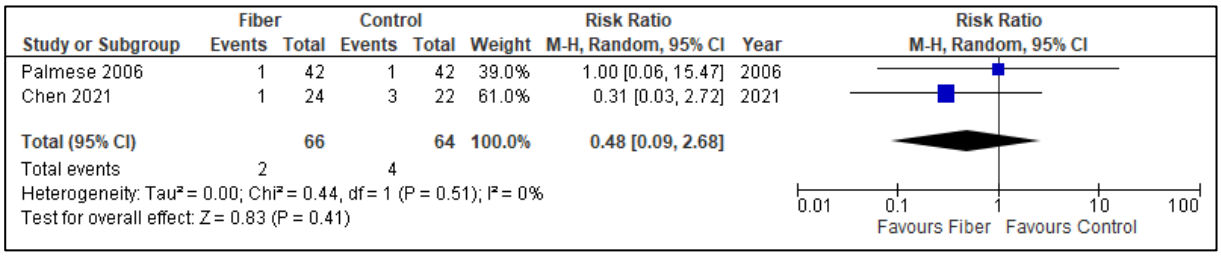
6b) Pneumonia



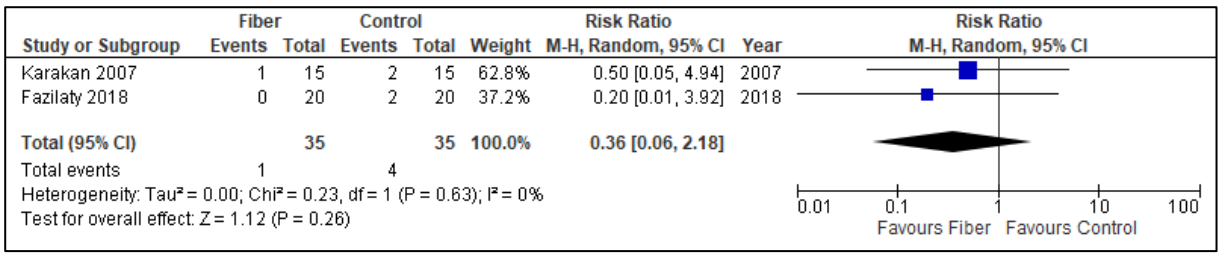
6c) Urinary tract infection



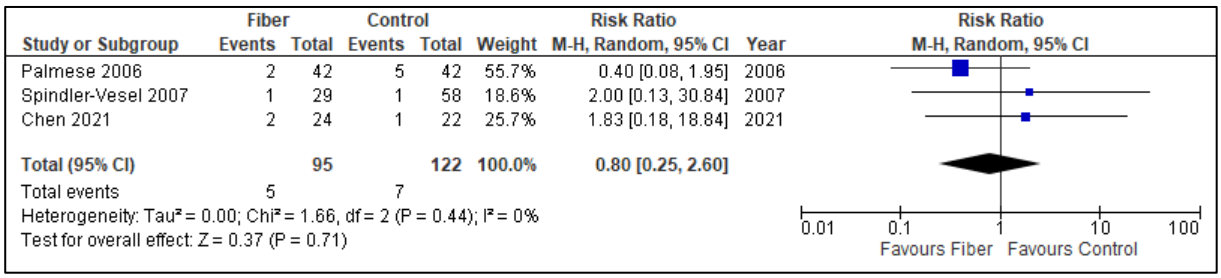
6d) Intra-abdominal infection



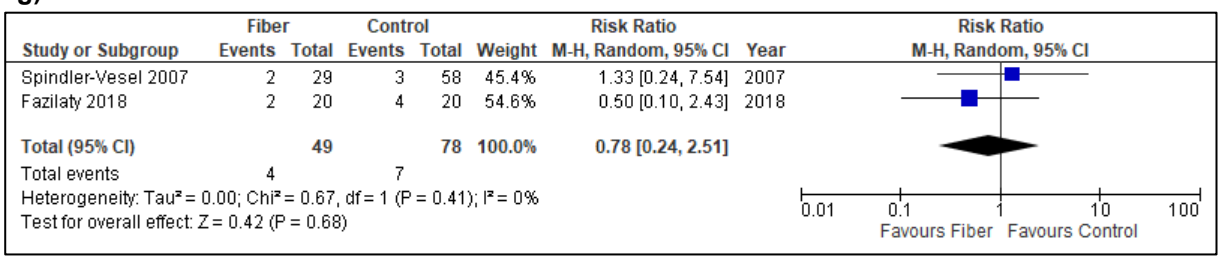
6e) Sepsis



6f) Vascular infection



6g) Wound infection



6h) Bacteremia

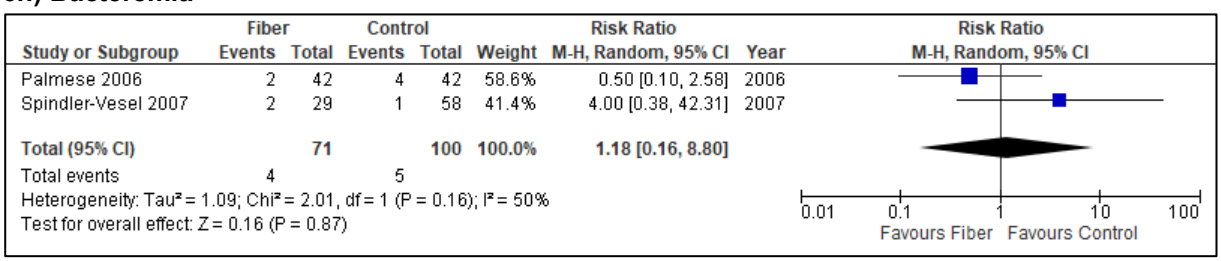


Figure S7: Duration of mechanical ventilation

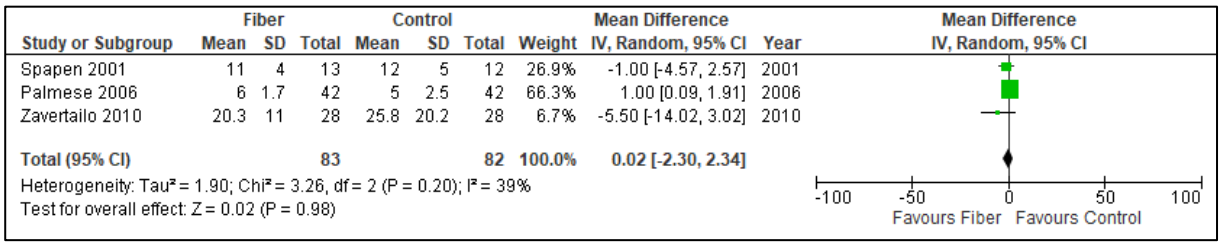
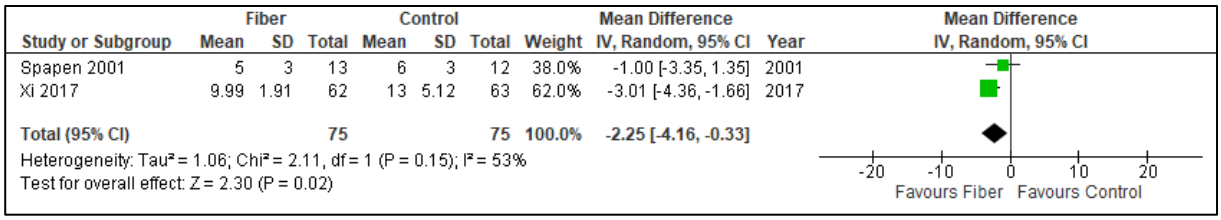
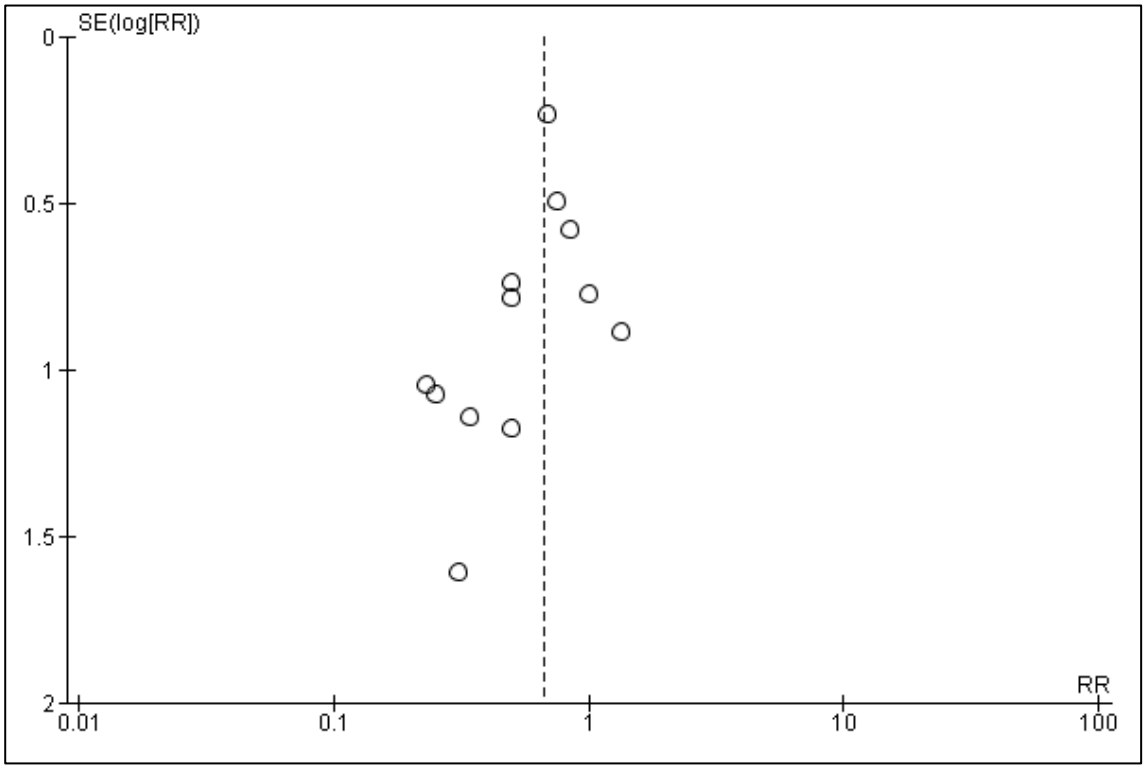


Figure S8: Time to reach target energy needs



PART 3C: Funnel plots

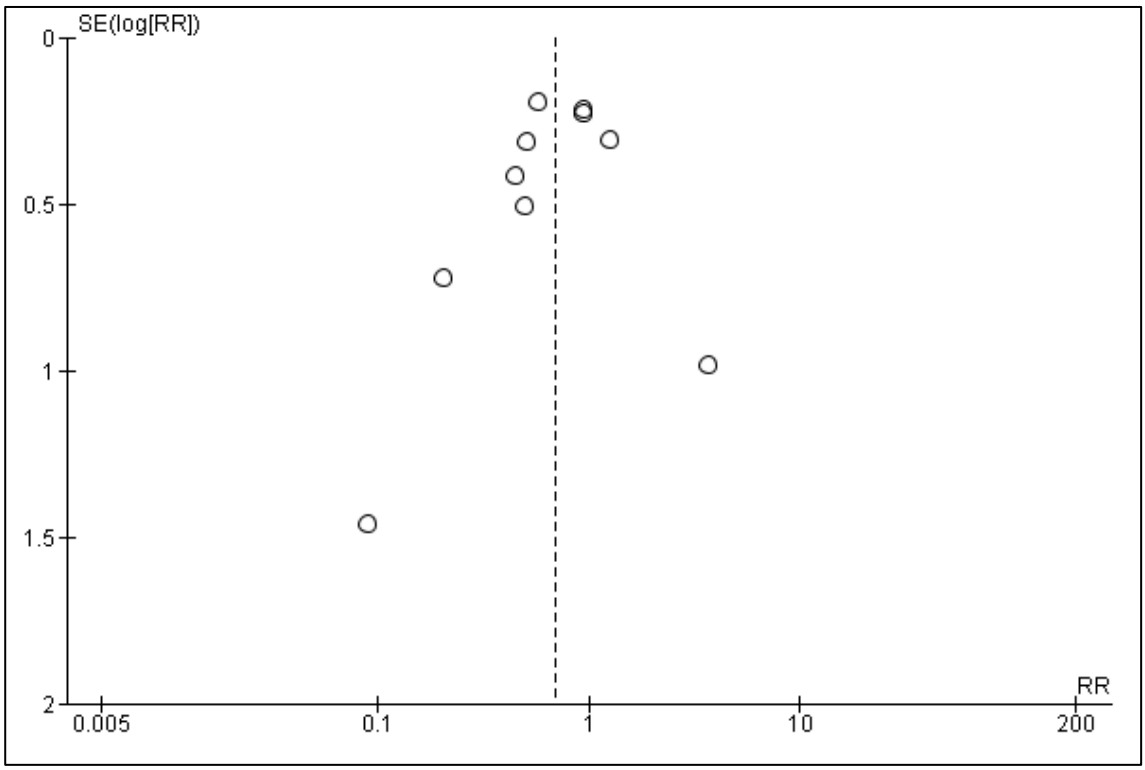
Figure S9: Mortality



Egger's test: p = 0.1430498

Figure S10: Diarrhea

10a) Diarrhea incidence



Egger's test: p = 0.4083957

10b) Diarrhea score

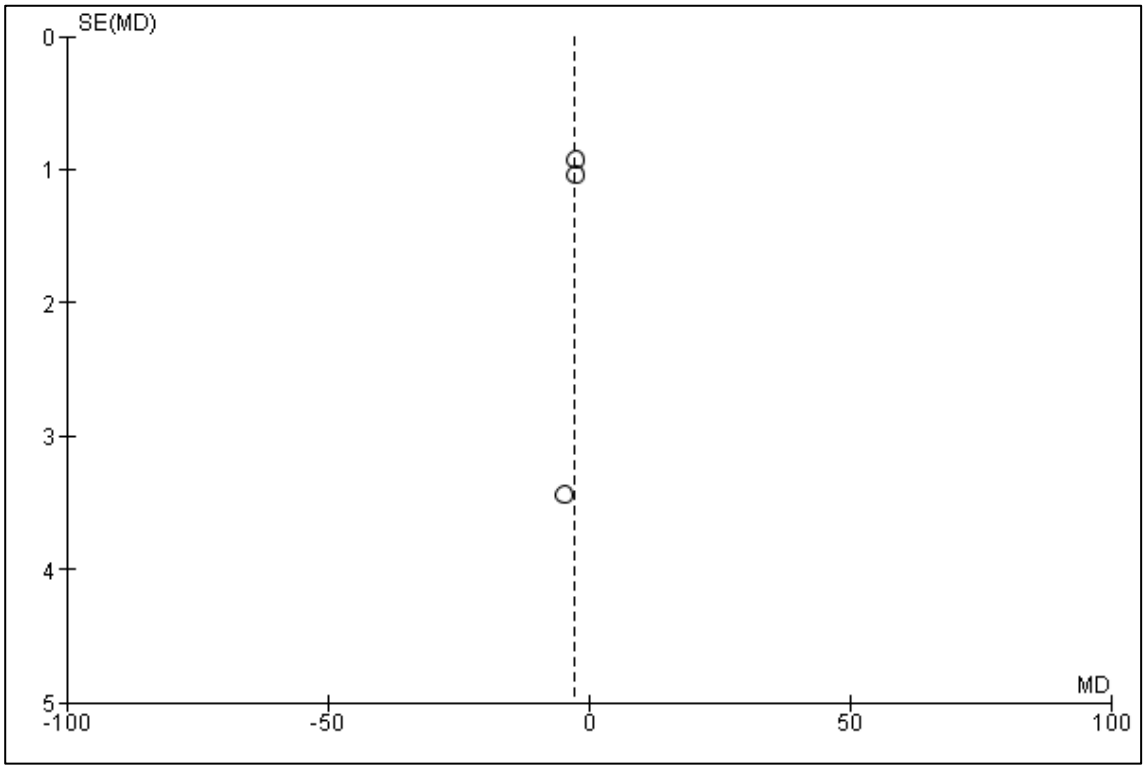
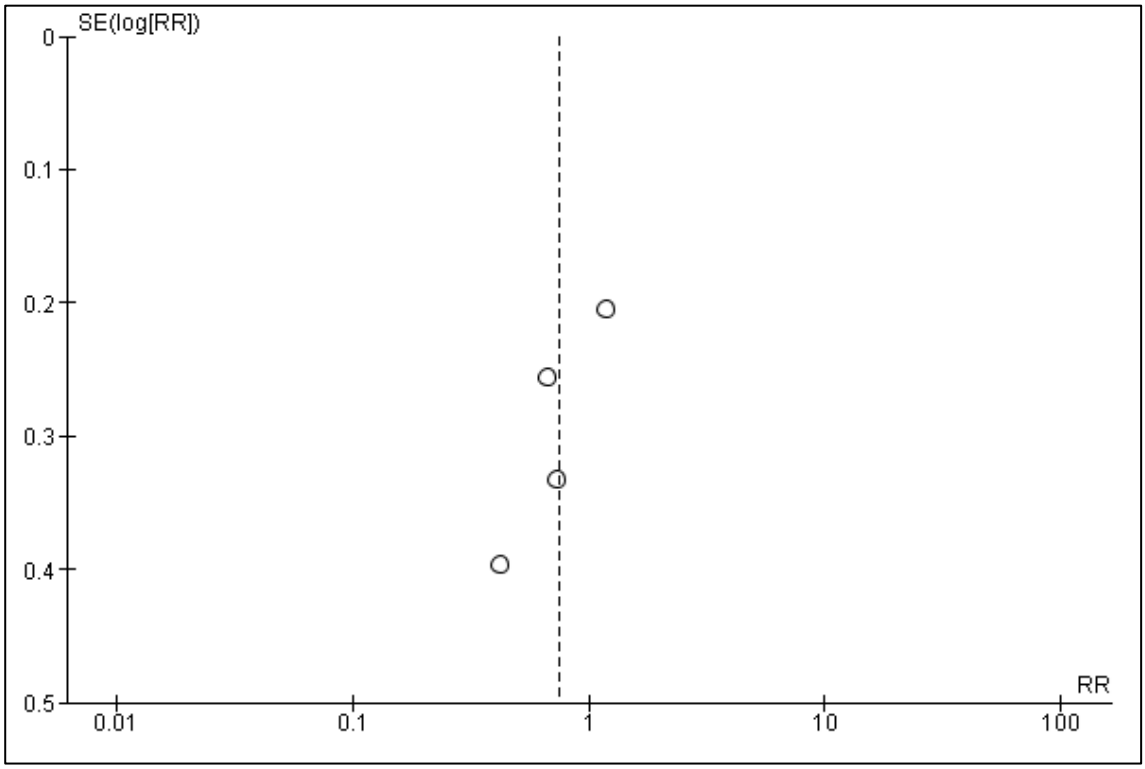
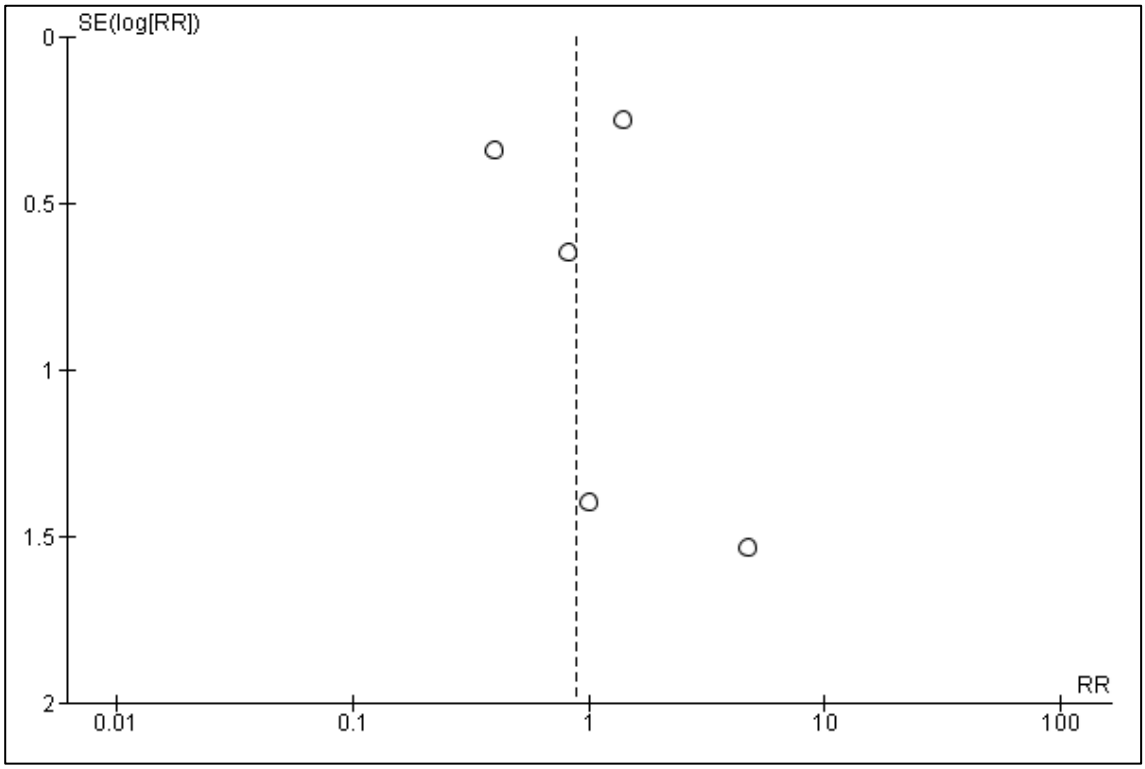


Figure S11: Other GI complications

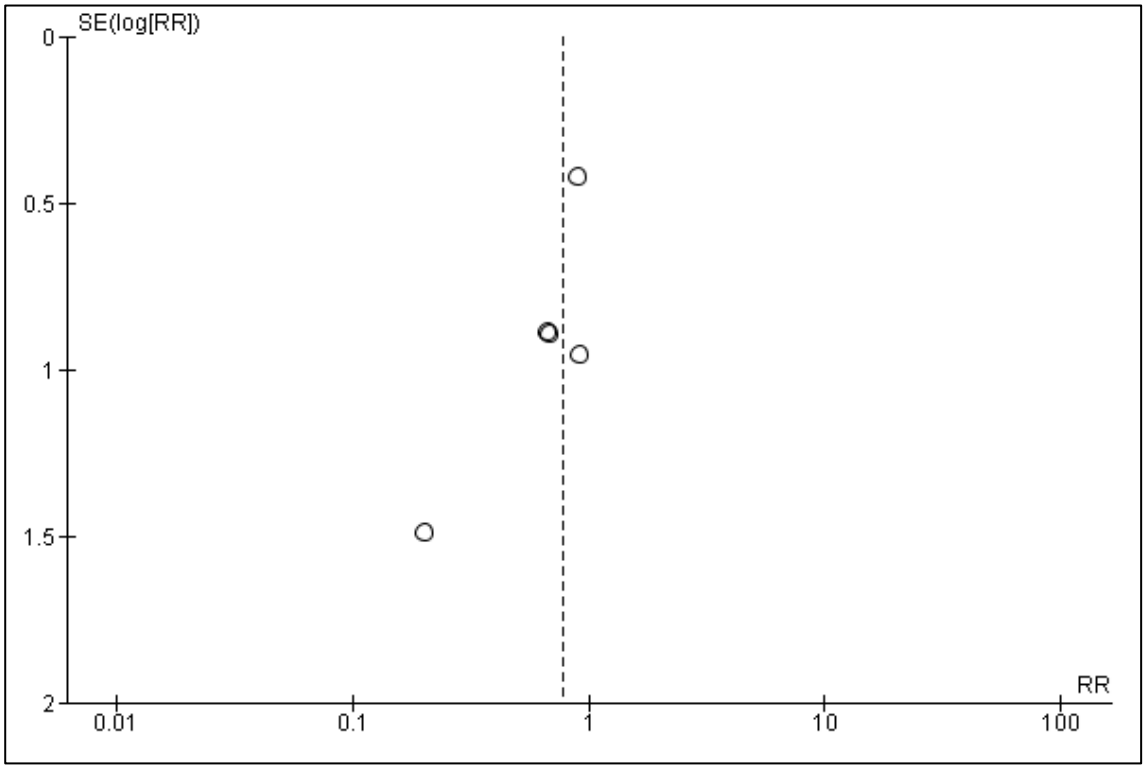
11a) Patients with at least 1 GI complication



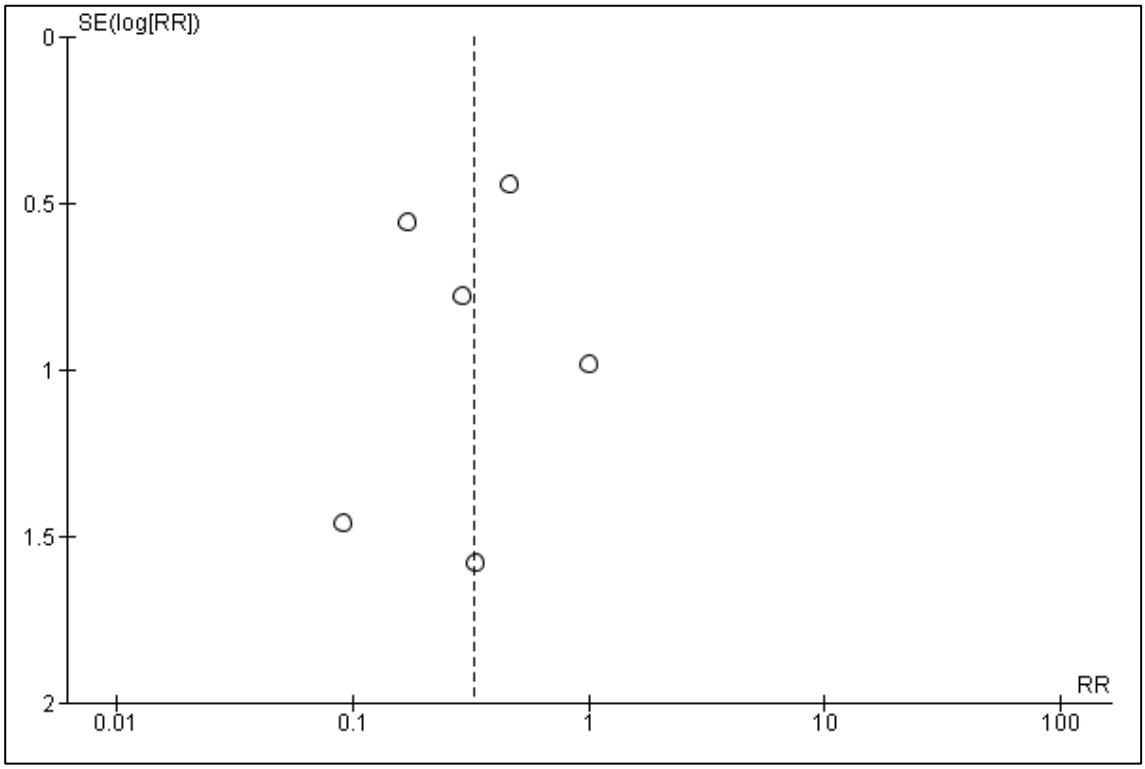
11b) Abdominal distension



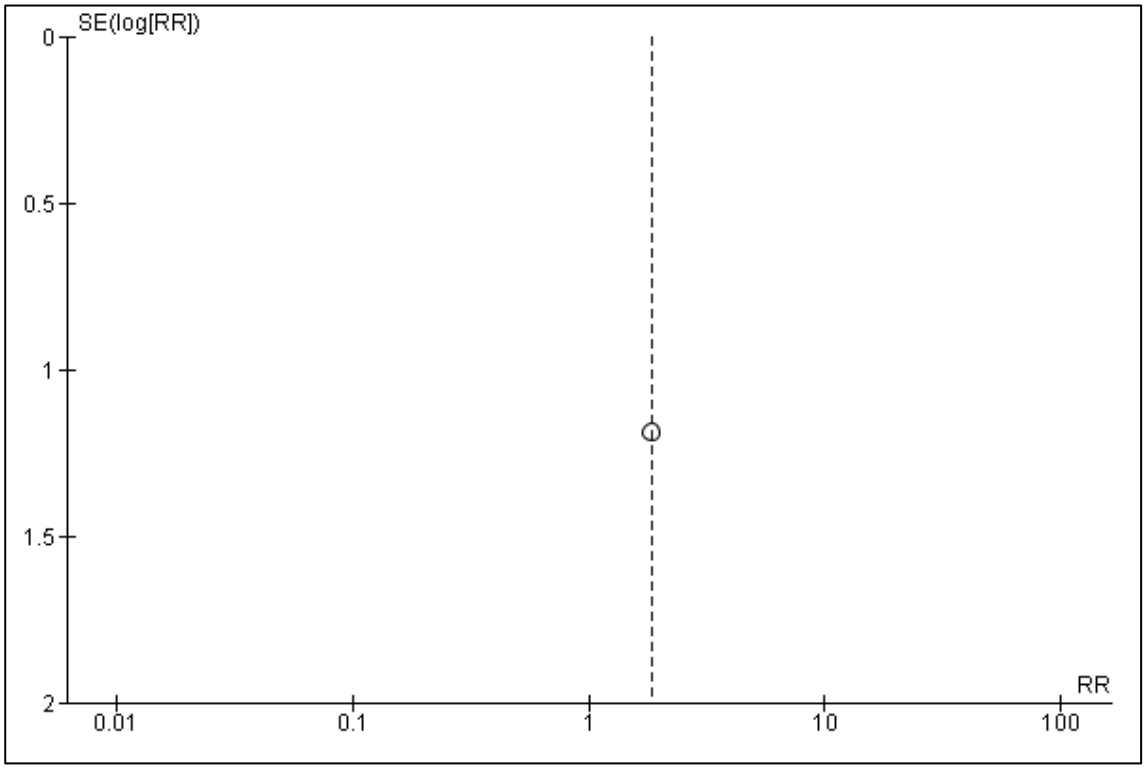
11c) Vomiting



11d) Constipation



11e) GI bleeding



11f) Regurgitation

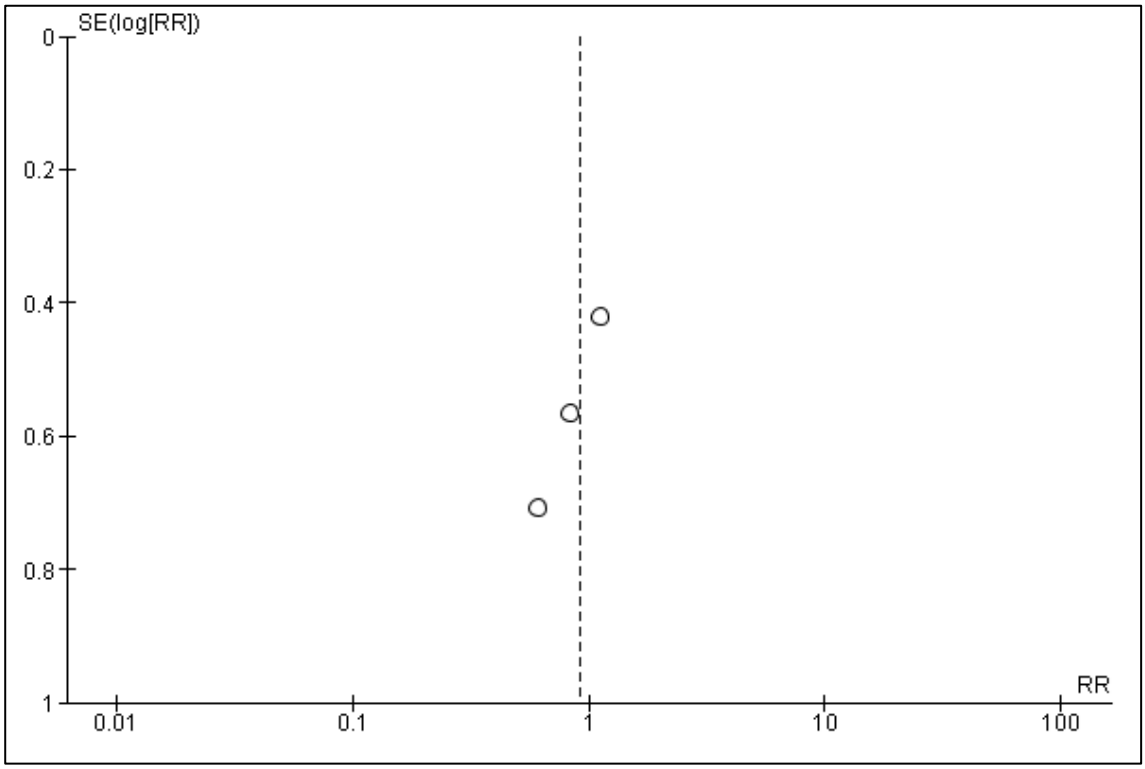


Figure S12: ICU length of stay

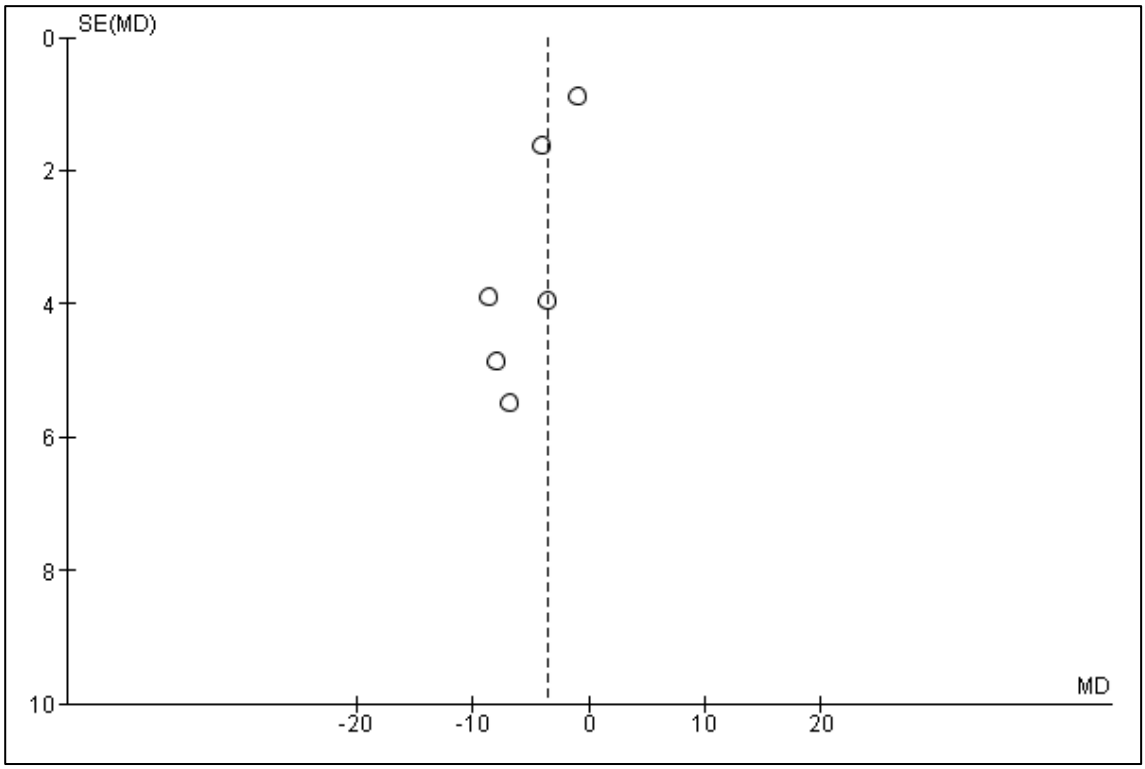


Figure S13: Hospital length of stay

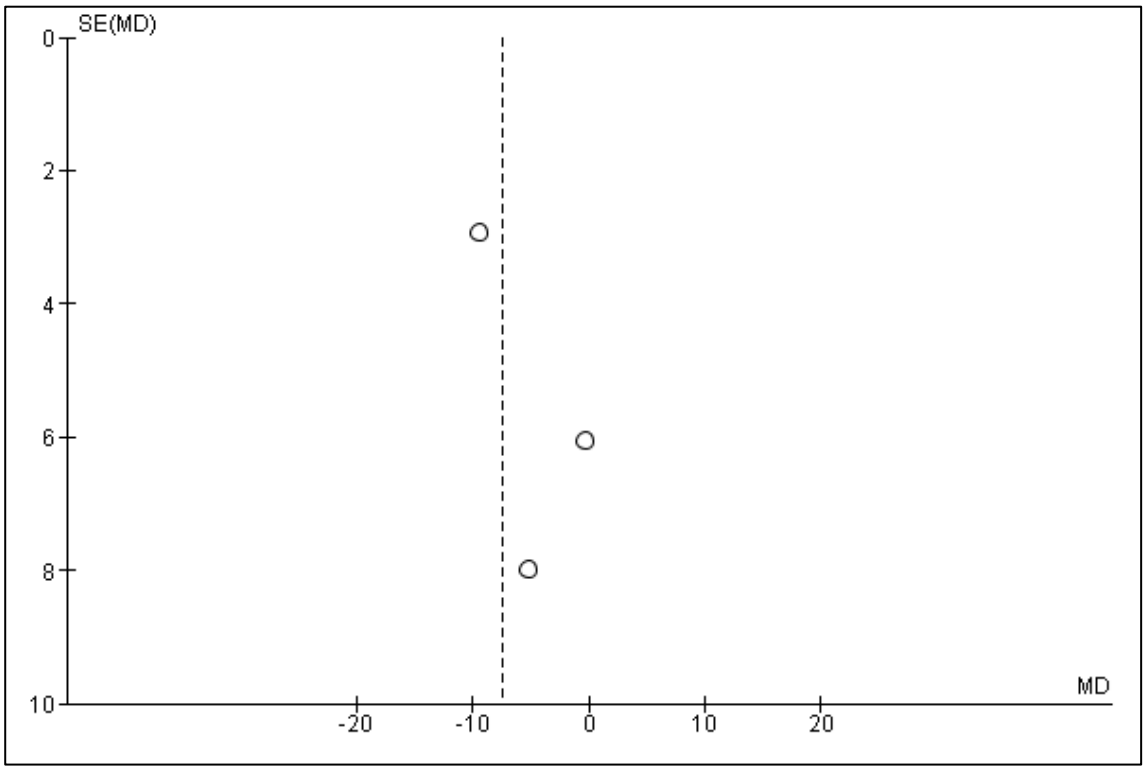
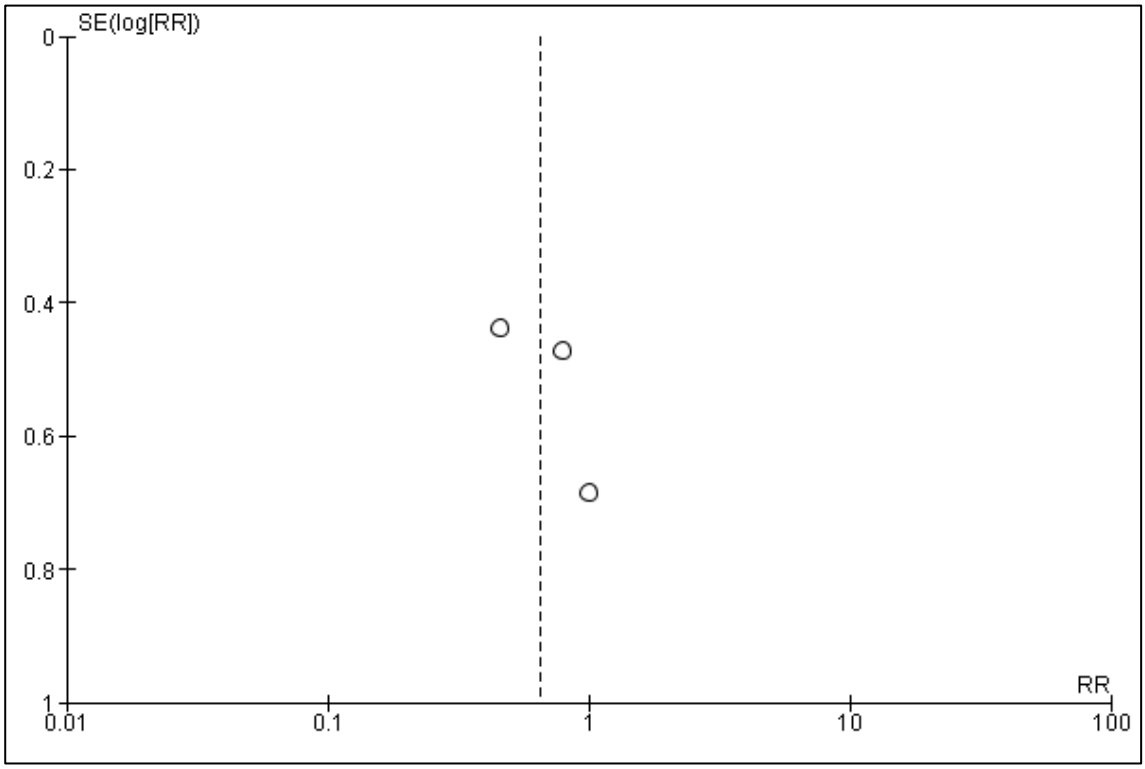
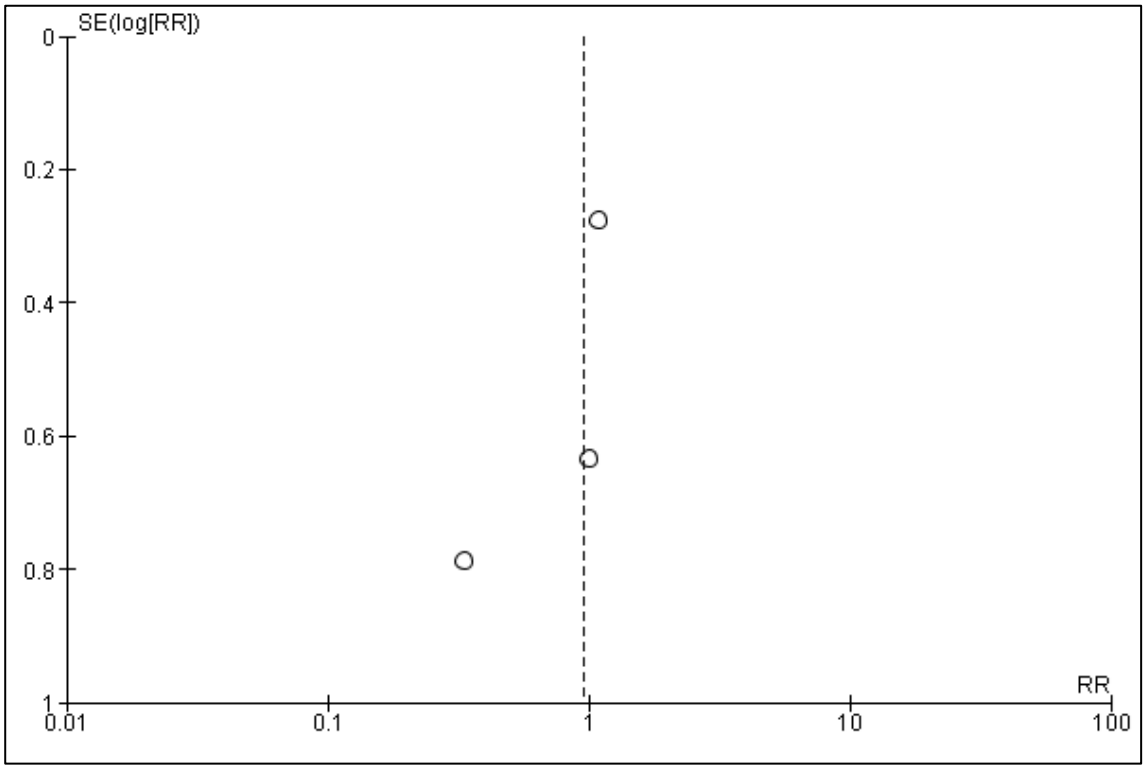


Figure S14: Infectious complications

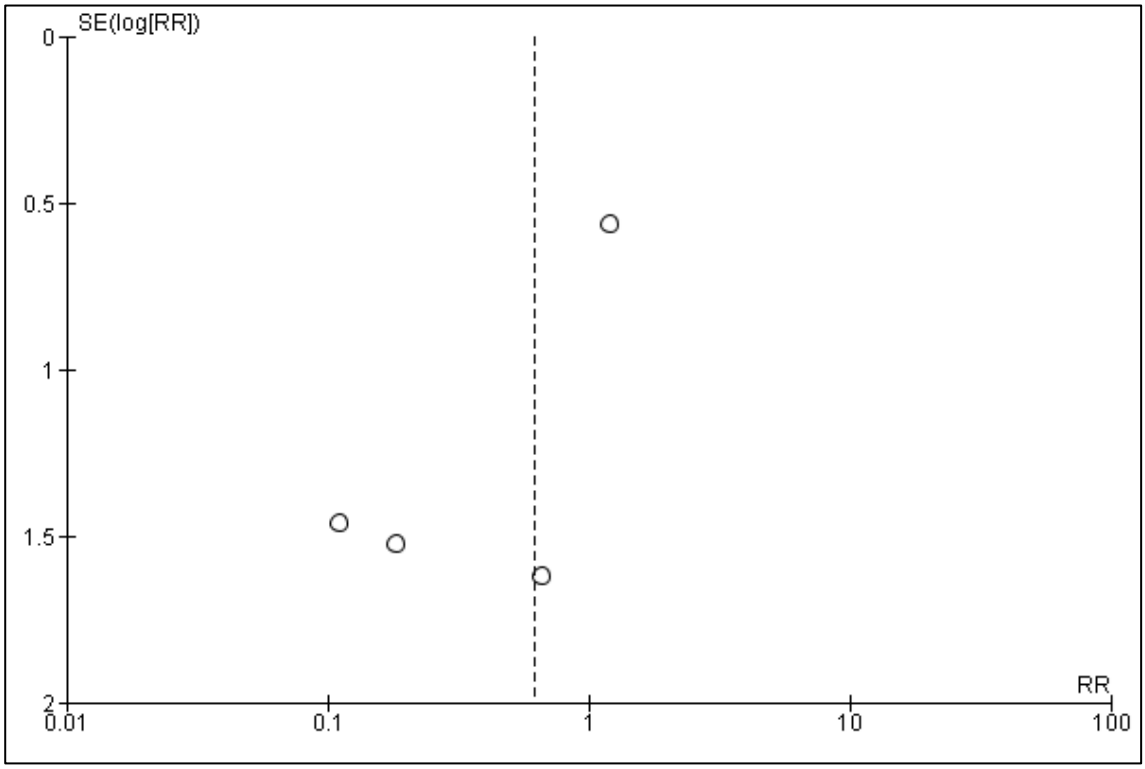
14a) Patients with at least 1 infectious complication



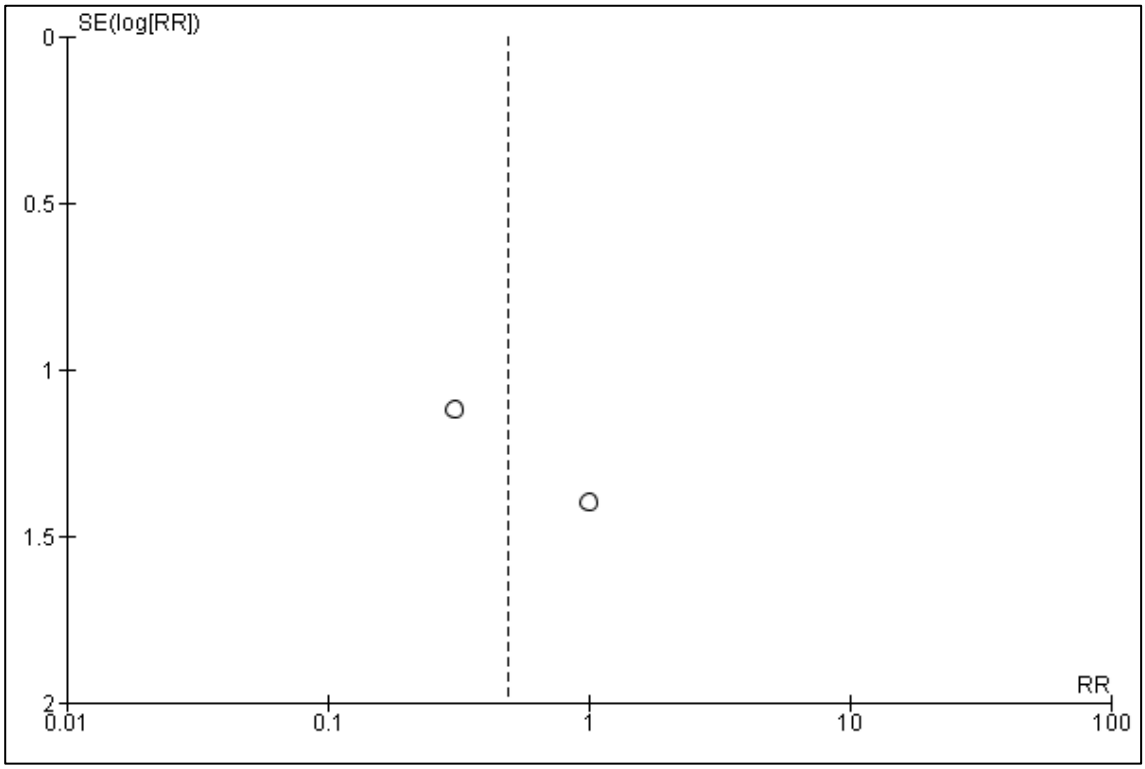
14b) Pneumonia



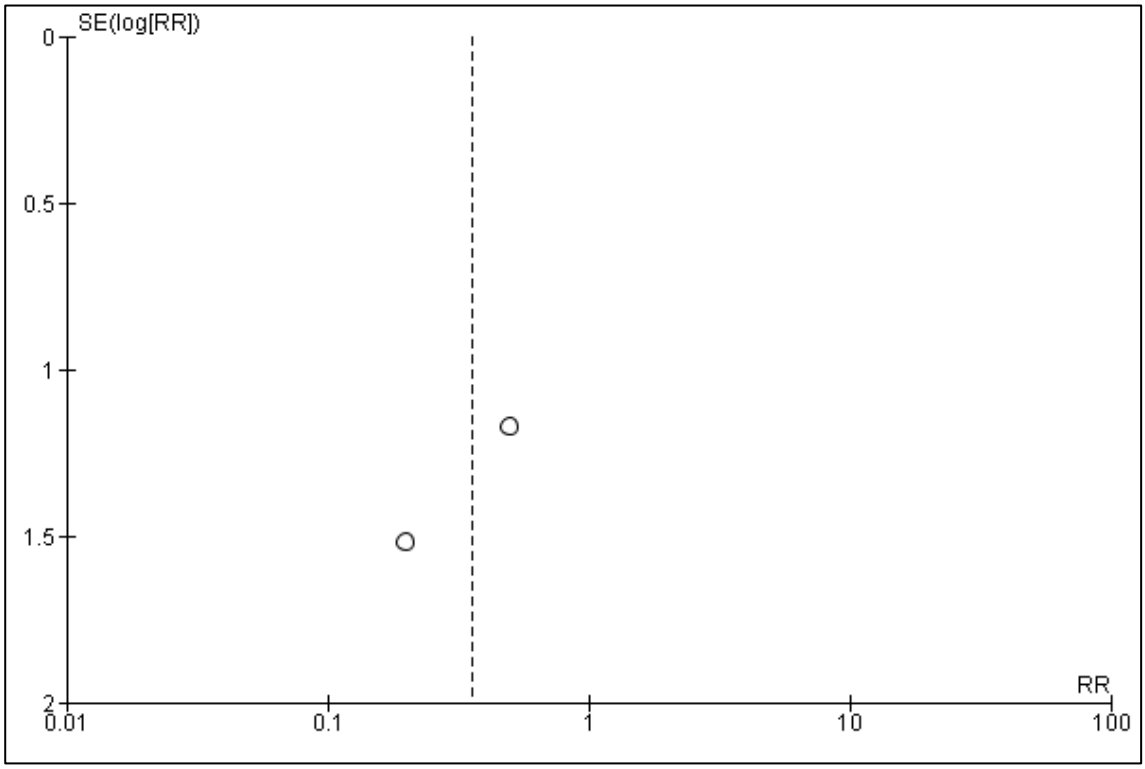
14c) Urinary tract infection



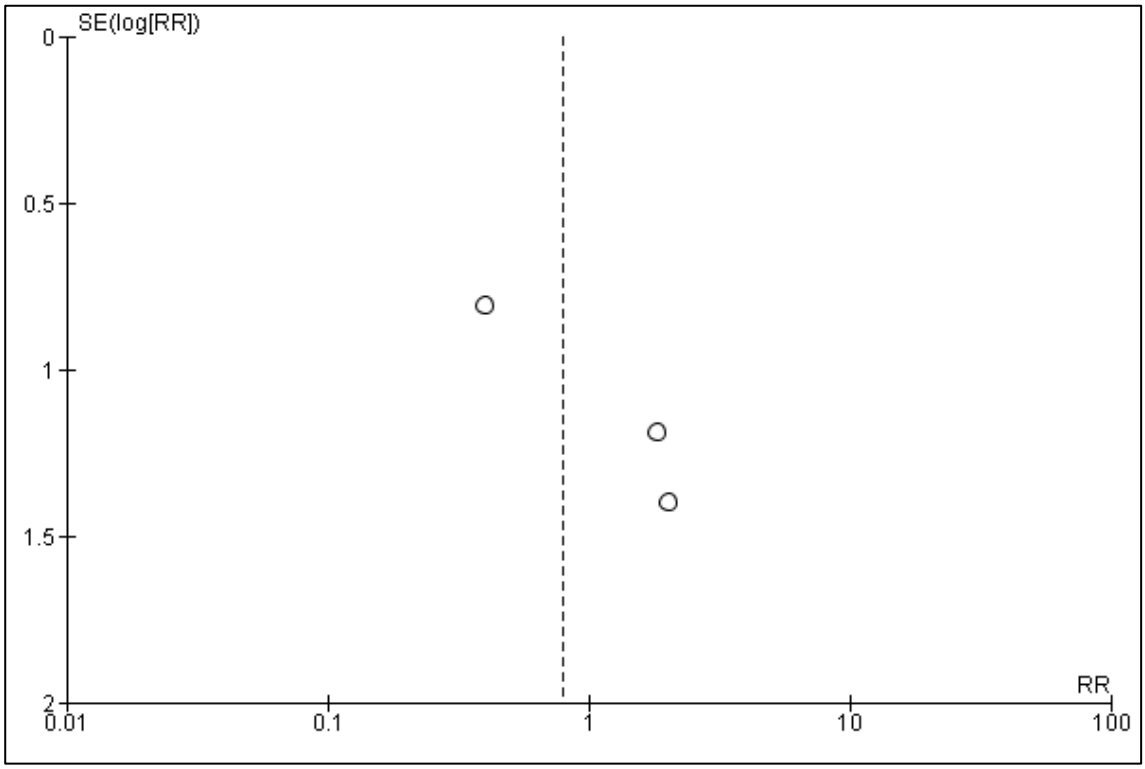
14d) Intra-abdominal infection



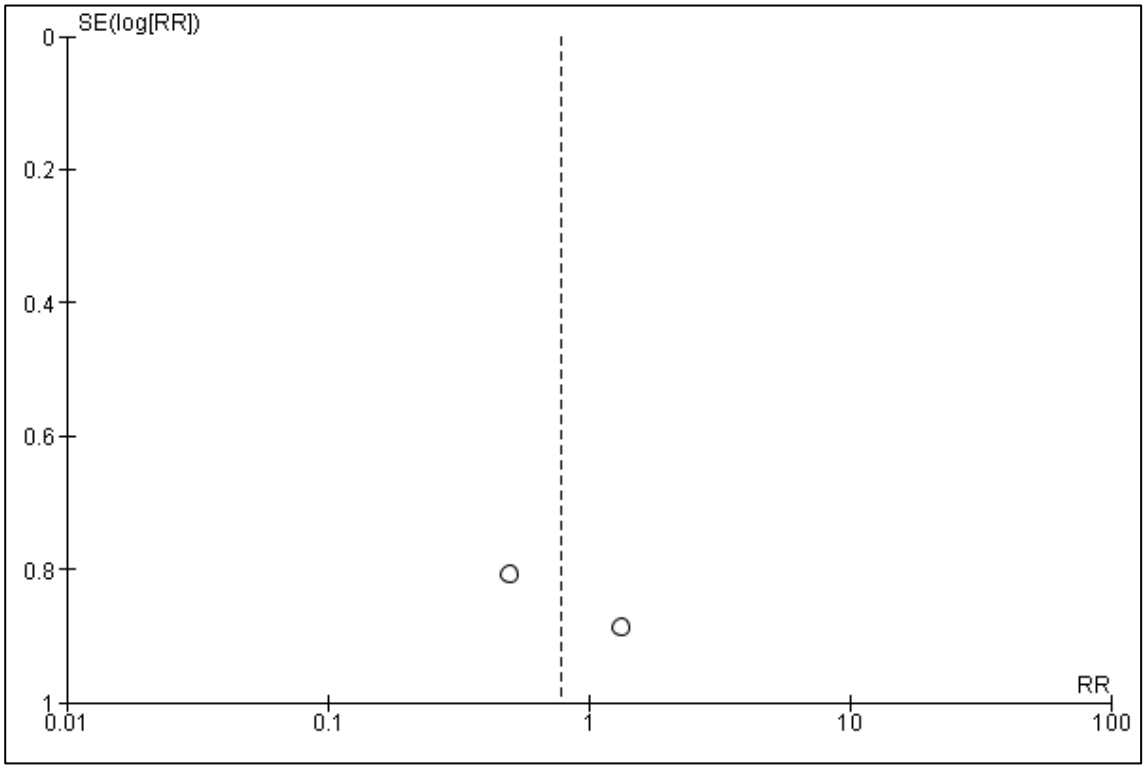
14e) Sepsis



14f) Vascular infection



14g) Wound infection



14h) Bacteremia

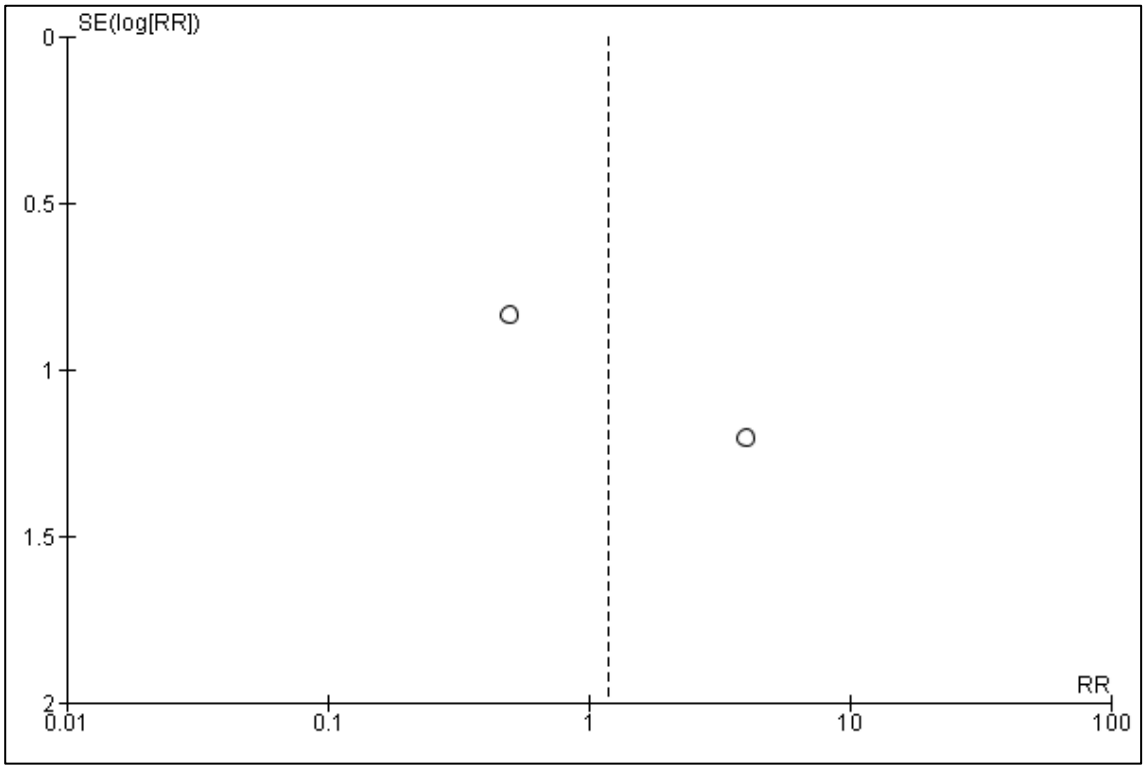


Figure S15: Duration of mechanical ventilation

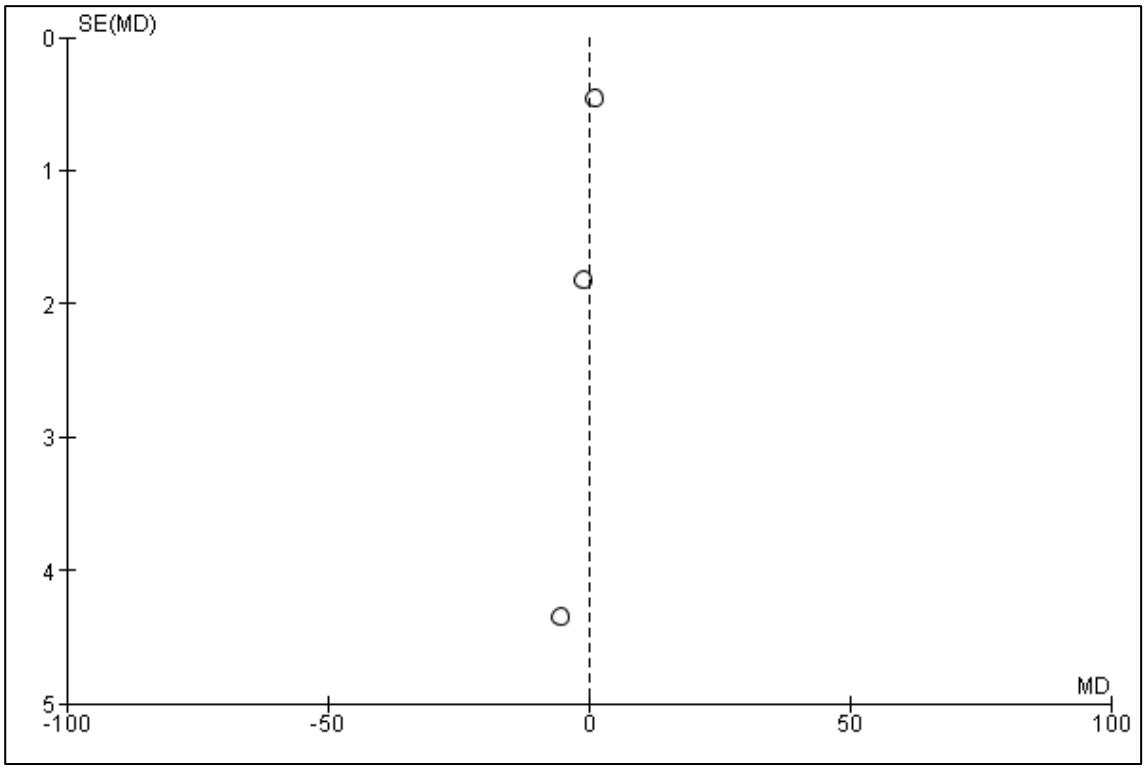
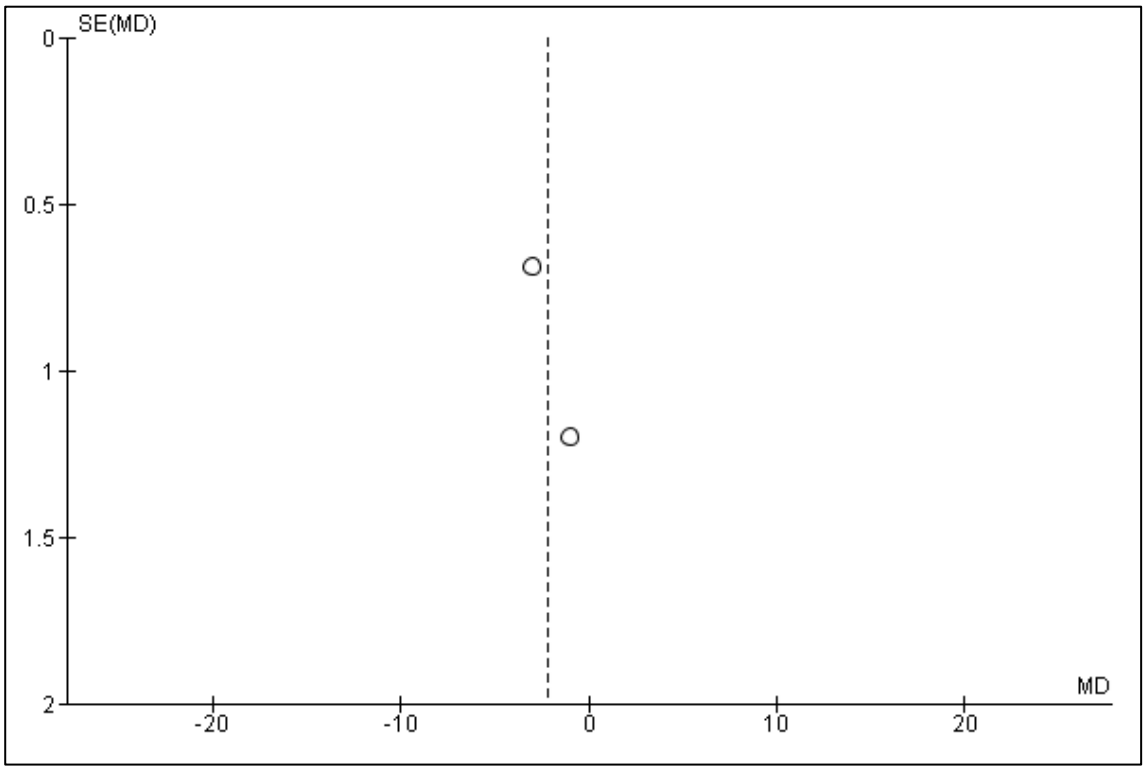


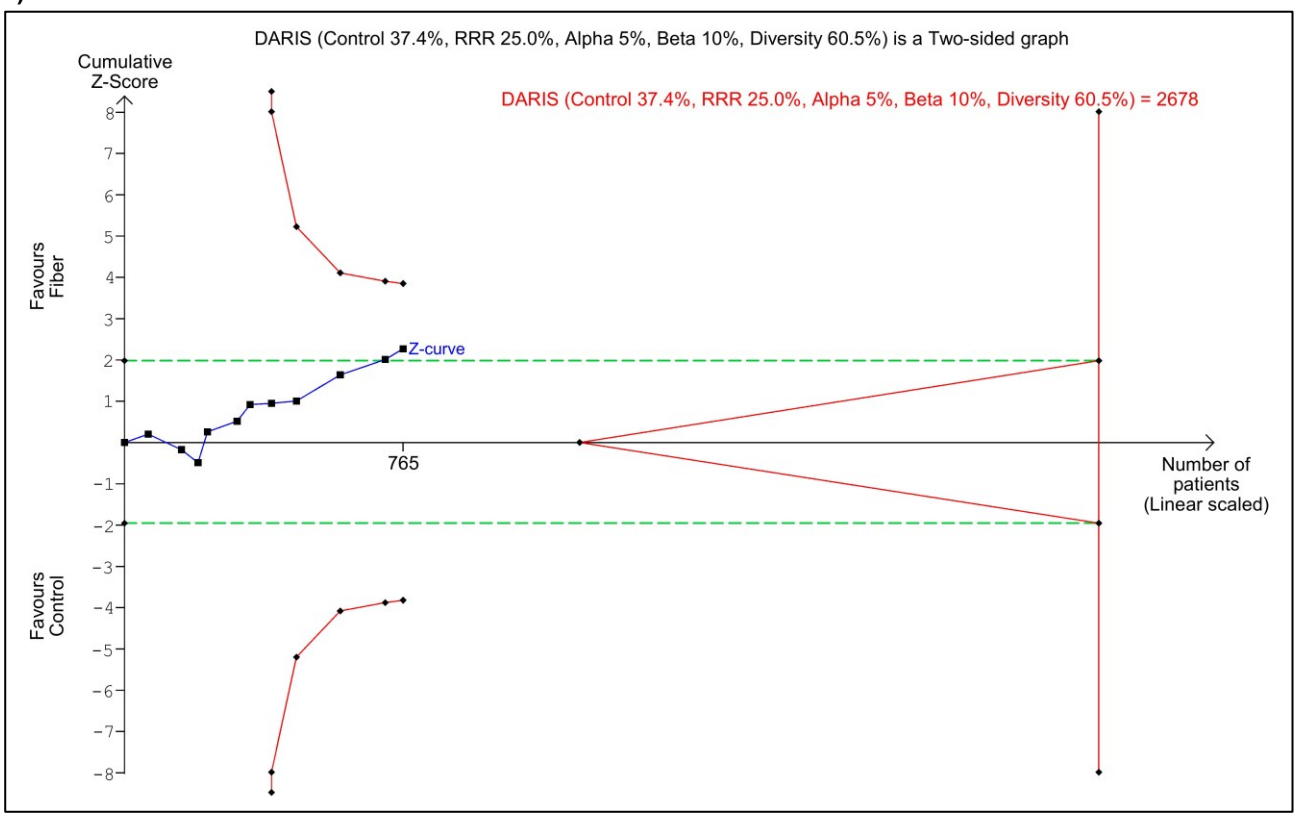
Figure S16: Time to reach target energy needs



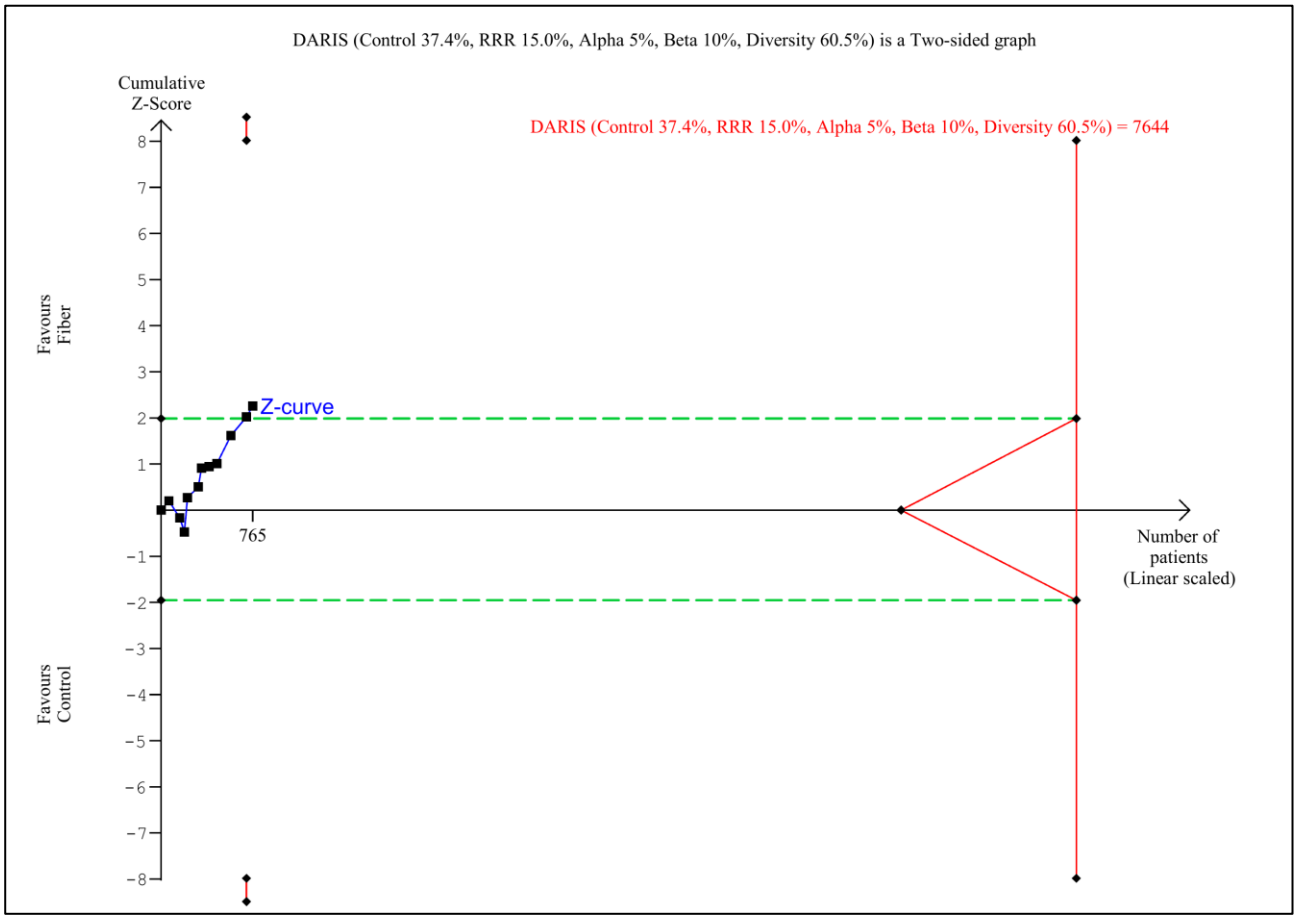
PART 4: Trial Sequential Analysis

Fig. S17: Diarrhea incidence

a) RRR = 25%



b) sensitivity analysis – RRR = 15%



c) sensitivity analysis – RRR = 35%

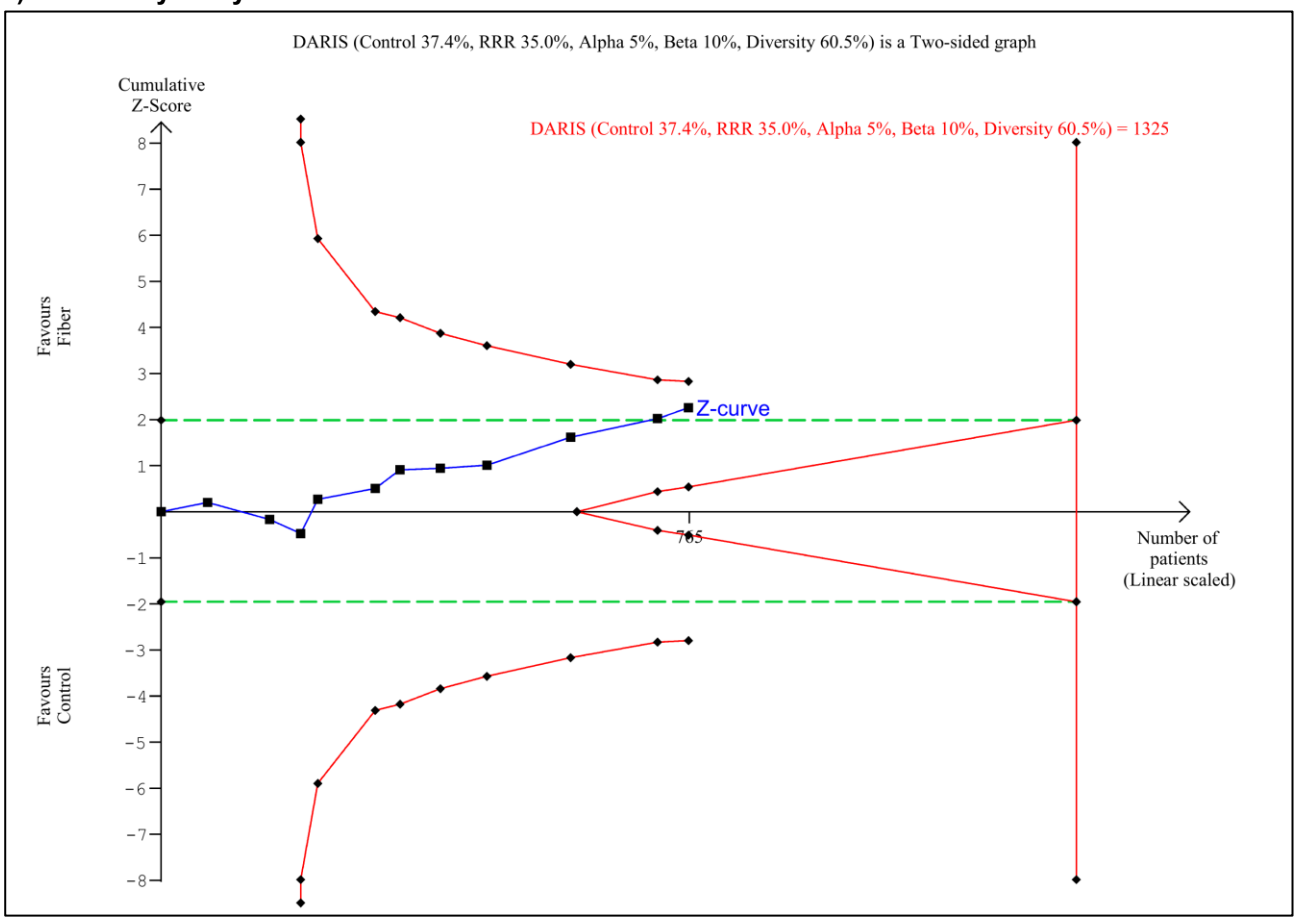
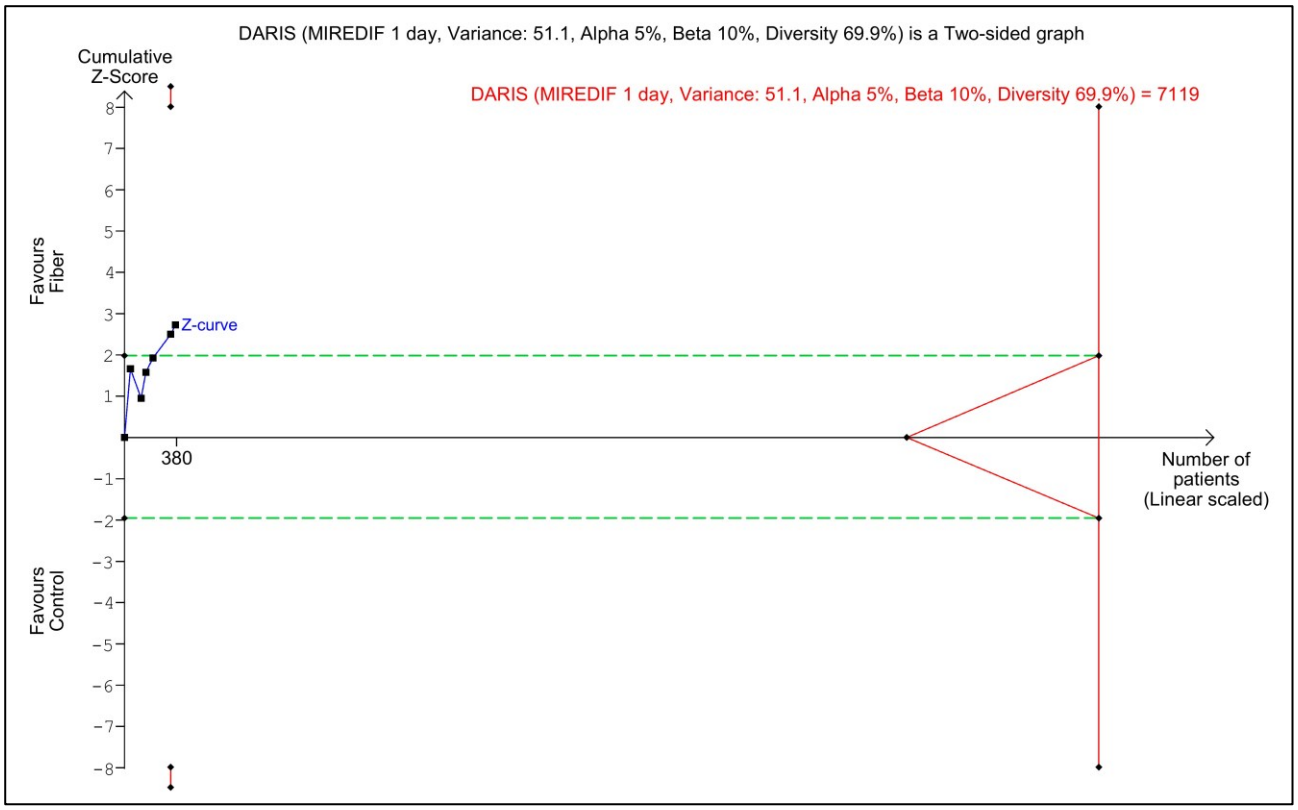
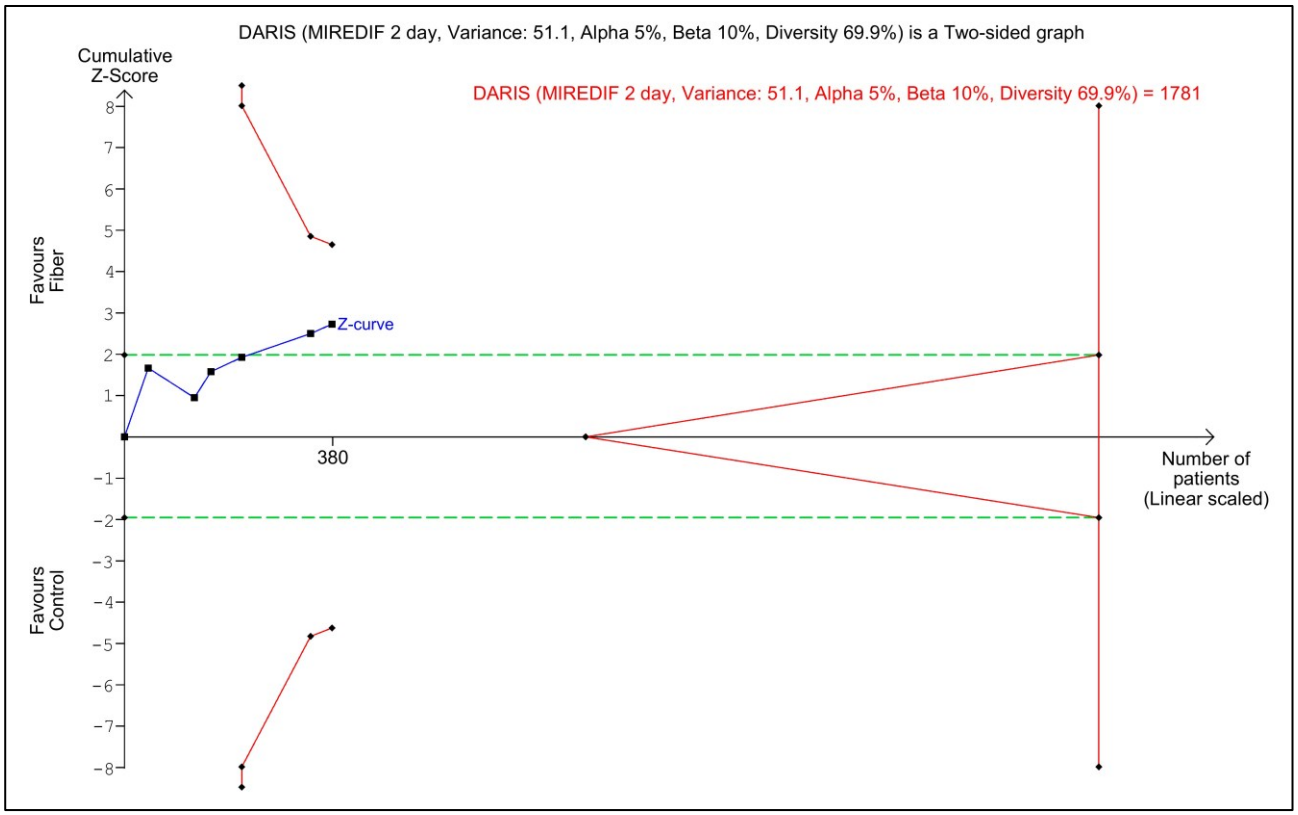


Fig. S18: ICU LOS with sensitivity analyses

a) MIREDIF = 1 day



b) sensitivity analysis – MIREDIF = 2 days



c) sensitivity analysis – MIREDIF = 3 days

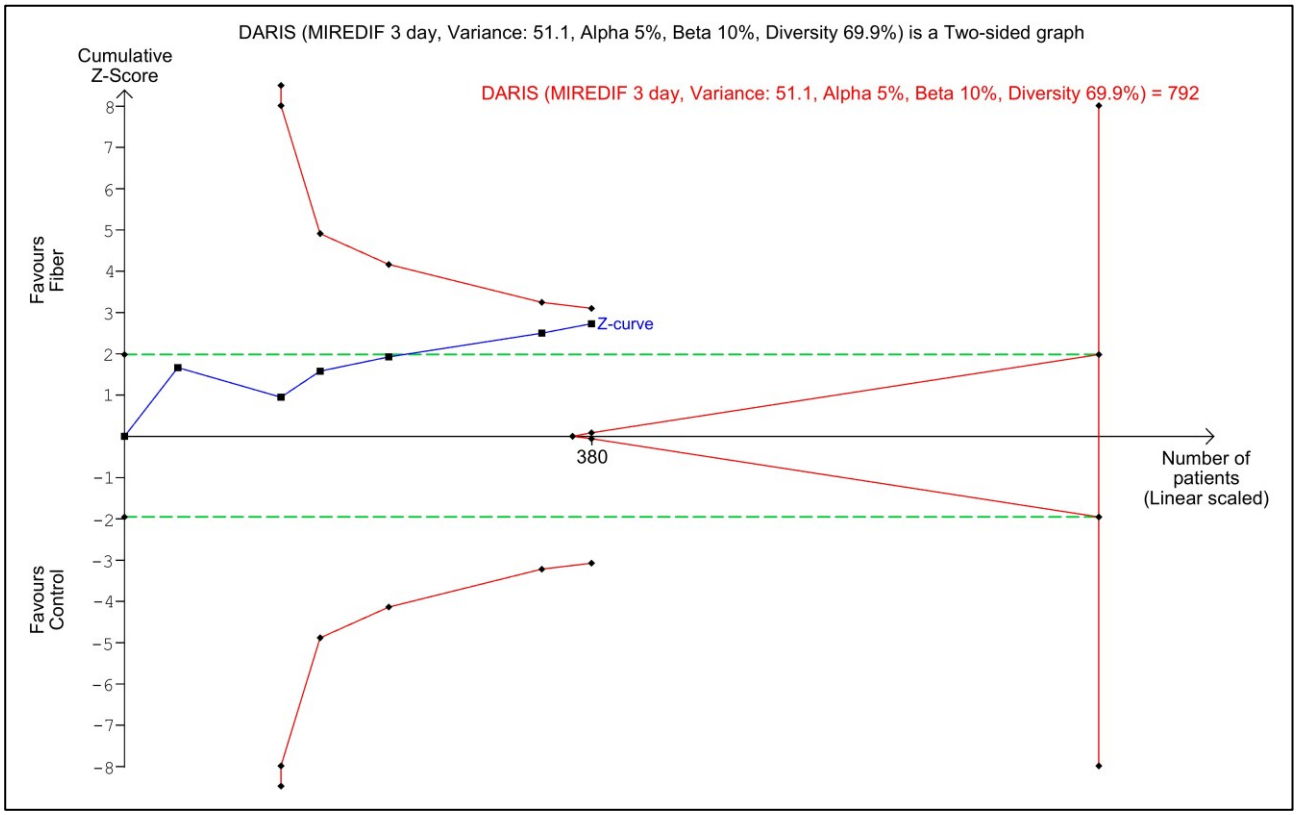
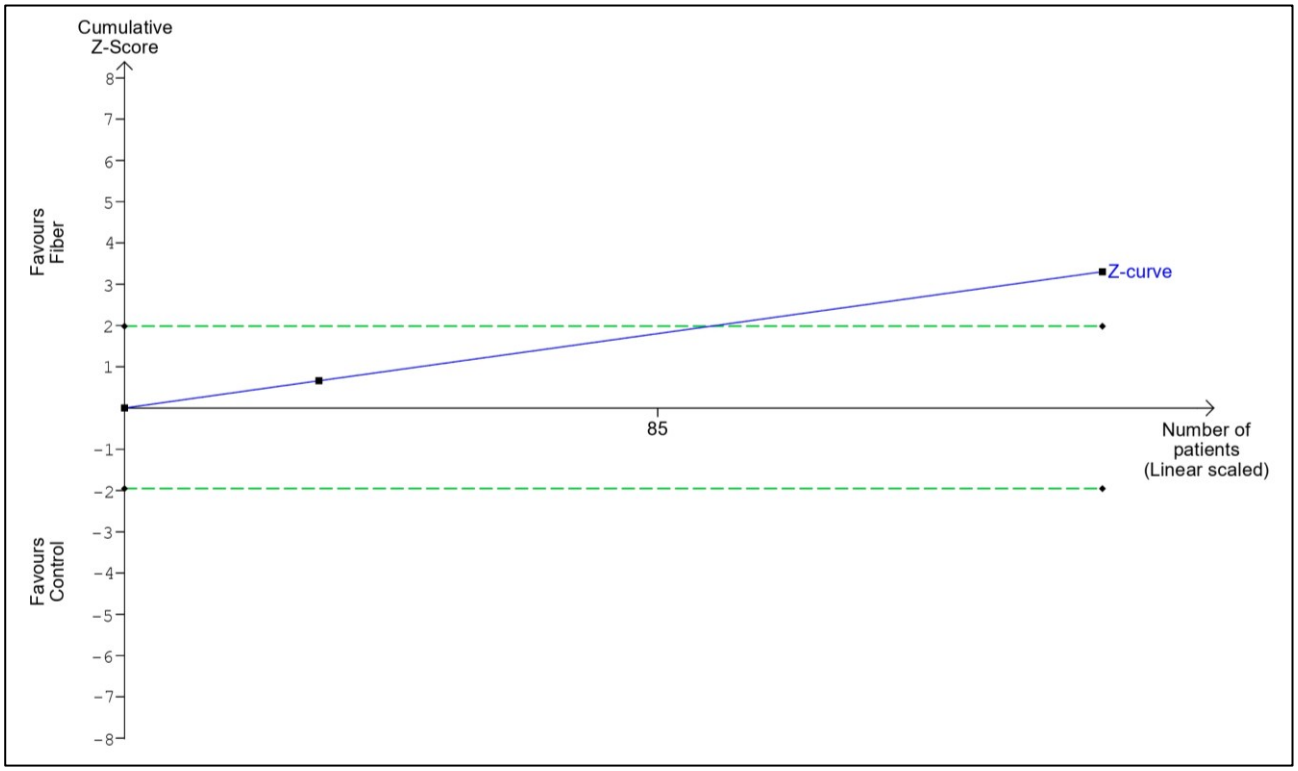
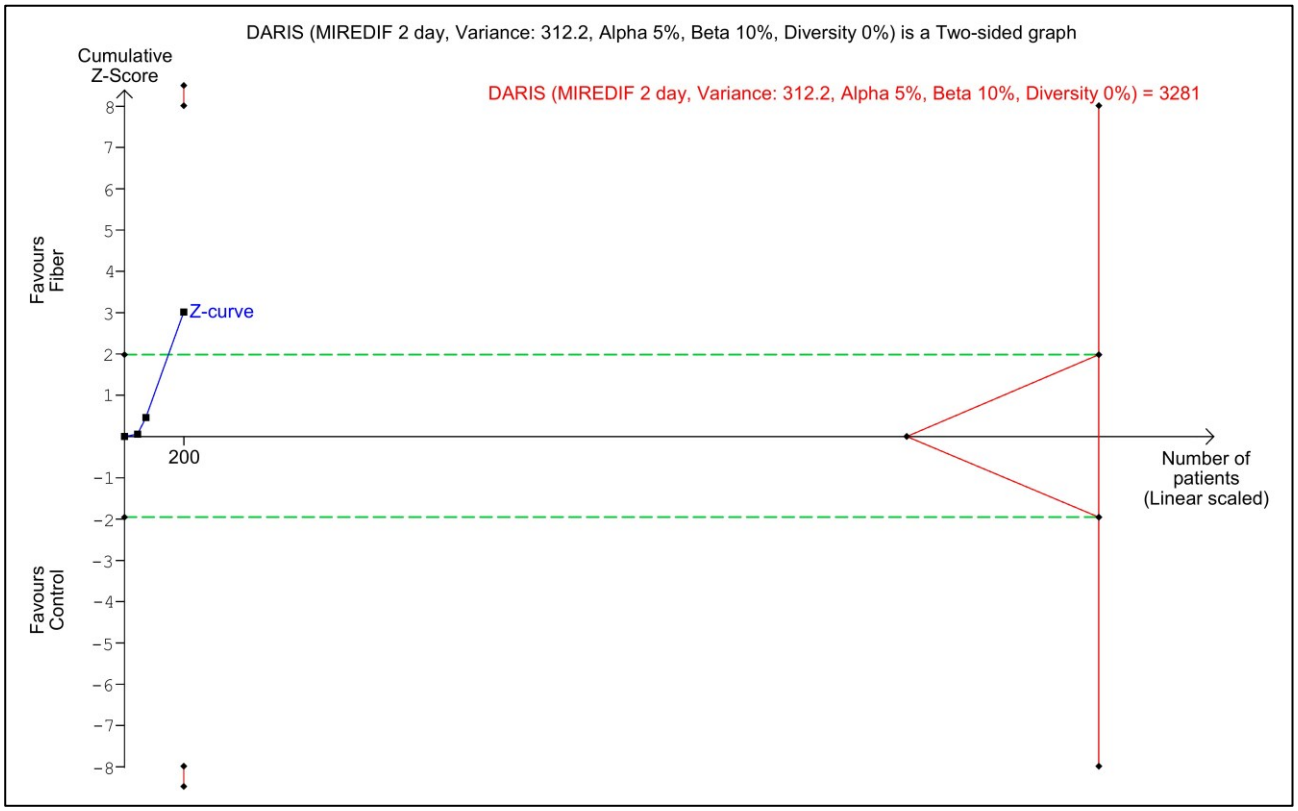


Fig. S19: Hospital LOS with sensitivity analyses

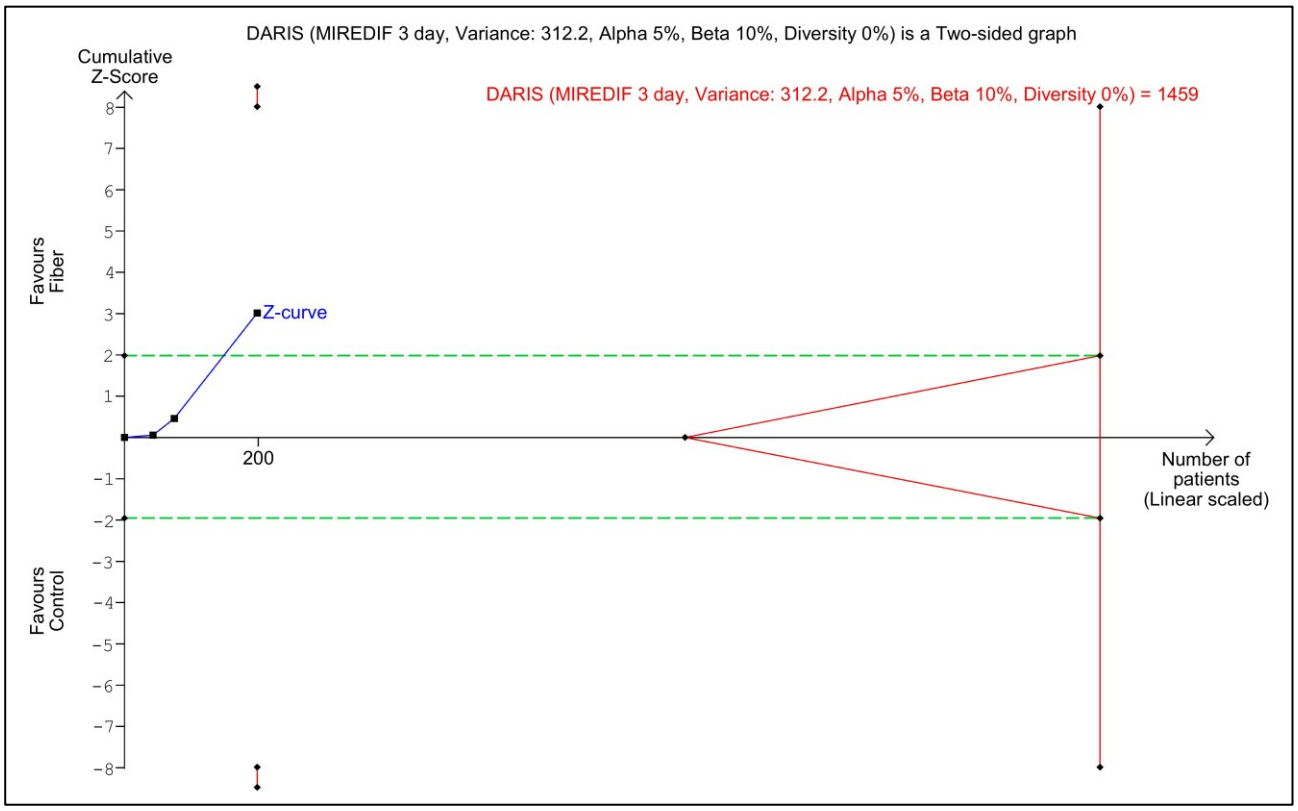
a) MIREDIF = 1 day



b) sensitivity analysis – MIREDIF = 2 days



c) sensitivity analysis – MIREDIF = 3 days



References

[1] J. Wetterslev, J. C. Jakobsen, and C. Gluud, "Trial Sequential Analysis in systematic reviews with meta-analysis," (in eng), *BMC Med Res Methodol,* vol. 17, no. 1, p. 39, Mar 6 2017, doi: 10.1186/s12874-017-0315-7.

Erklärung § 5 Abs. 1 zur Datenaufbewahrung

Hiermit erkläre ich, dass die dieser Dissertation zu Grunde liegenden Originaldaten

bei mir, **Jana Larissa Koch,**

hinterlegt sind.

Erklärung gemäß § 5 Abs. (1) und (2), und § 11 Abs. (3) 12. der Promotionsordnung

Hiermit erkläre ich, **Jana Larissa Koch**, an Eides statt, dass ich den wesentlichen Anteil an der Publikation:
Jana Larissa Koch, Charles Chin Han Lew, Felix Kork, Alexander Koch, Christian Stoppe, Daren K. Heyland, Ellen Dresen, Zheng-Yii Lee & Aileen Hill: The efficacy of fiber-supplemented enteral nutrition in critically ill patients: a systematic review and meta-analysis of randomized controlled trials with trial sequential analysis; Critical Care; 2024, 28:359 geleistet habe.
Die Anteile an der Arbeit waren wie folgt:

	Jana Larissa Koch	Charles Chin Han Lew	Felix Kork	Alexander Koch	Christian Stoppe	Daren K. Heyland	Ellen Dresen	Zheng-Yii Lee	Aileen Hill	Summe (%)
Studienüberwachung			5	5				10	80	100
Studiendesign/Konzeption	25	5	5	5	5	5	5	20	25	100
Datenerhebung	50								50	100
Datenauswertung	70							15	15	100
Statistische Auswertung	90	10								100
Bereitstellung von Materialien	20	10	5	5				30	30	100
Interpretation der Datenauswertung	35	15			5	5		20	20	100
Verfassung des Manuskripts	**100**									100
Korrektur des Manuskripts		15	5	5	10	5	5	20	35	100

Aus diesem wesentlichen Anteil ergibt sich selbstverständlich die Stellung als Erstautorin.

_____
Unterschrift der Doktorandin

Als Doktormutter und korresp. Autorin bestätige ich die Angaben von Jana Larissa Koch und in Vertretung für die **nicht deutschsprachigen** Koautoren Daren K. Heyland, Zheng-Yii Lee und Charles Chin Han Lew.

_____ _____
Unterschrift der Doktormutter Unterschrift des korresp. Autors (falls abweichend)

Ich schließe mich der Erklärung von Priv.-Doz. Dr. med. Aileen Hill als Koautor an

_____
Namen und Unterschriften aller deutschsprachigen Koautoren (auf separaten Seiten, aber immer mit Tabelle, möglich)

Alle Unterschriften müssen auf der Seite stehen, auf dem sich auch der Text der Erklärung befindet (hierzu die Erklärung ggf. mehrfach ausdrucken), so dass eindeutig ist, dass die Autoren den Text der eidesstattlichen Erklärung unterschrieben haben. Die Unterschriften der Doktorandin/des Doktoranden, des Doktorvaters, des Seniorautors (korrespondierenden Autors) (falls abweichend vom Doktorvater) und des gleichberechtigten Erstautors (falls zutreffend) müssen im Original eingereicht werden.