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a systematic review

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Abstract

Nutritional interventions in randomised clinical trials for people with incurable solid cancer: a systematic review

Background & aims: Malnutrition is highly prevalent in those with cancer and more so in those with incurable cancer. In incurable cancer, it is widely agreed that optimal nutritional care has the potential to positively impact patient and caregiver distress and oncological outcomes. The aim of this systematic review was to describe the diversity and frequency of nutritional interventions, whether given in isolation or as part of a multimodal intervention in those with incurable cancer, in randomised controlled trials. The secondary aims were to describe adherence and their efficacy.

Methods: This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. The following databases were searched electronically: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), Cumulated Index to Nursing and Allied Health Literature (CINAHL) and Cochrane Central Register of Controlled Trials (CENTRAL) with the time frame from January 2000 to 7th September 2023. Eligible studies included adult patients (≥ 18 years) diagnosed with incurable solid cancer with a sample size ≥ 40. Studies were to be primary research and delivered for at least 14 days to allow for efficacy. They were to include a nutritional intervention encompassing at least one of the following: dietary counselling, oral nutritional supplements (ONS), enteral tube feeding and/or parenteral nutrition (PN), given in isolation or as part of a multi-modal intervention. Studies were excluded if the population contained patients who had completed curative

48 treatment or are being treated with curative intent, haematological cancers, or if they
49 examined the effects of micronutrients, proteins, amino acids or fatty acids given in isolation.
50 The quality of the included studies was assessed using the Cochrane risk of bias tool for
51 randomised trials (RoB2). A balloon plot was produced to present the results in addition to a
52 table with a narrative summary of the primary outcomes.
53 *Results:* A total of 7968 studies were identified, of which 18 met the eligibility criteria. This
54 included 2720 study participants. The included studies comprised: multimodal interventions
55 (n=7), dietary counselling (n=2), nutritional supplementation with or without dietary
56 counselling (n=7) and PN (n=2). Primary outcomes included quality of life (QoL), body
57 composition and nutritional status. For QoL, this was reported in 15 studies, 4 studies showed
58 a significant improvement. Body composition was evaluated in 15 studies, 5 of which showed
59 a significant improvement in body weight and two in fat-free mass (FFM). Nutritional status
60 was reported in 6 studies with one showing a significant difference in Patient-Generated
61 Subjective Global Assessment (PG-SGA) score. The risk of bias was deemed 'low' in 6 studies,
62 with 'some concerns' in 10 studies and a 'high risk' in 2 studies. There was heterogeneity
63 between the studies.
64 *Conclusion:* This systematic review has highlighted some positive findings in regard to QoL,
65 body weight and nutritional intake. Optimum nutritional intervention was not identified.
66 Future studies should evaluate the effectiveness of earlier nutritional interventions at the
67 point of diagnosis, including regular reviews and the impact this has on nutritional outcomes,
68 QoL and overall survival (OS).
69

70 *Keywords:* Incurable cancer, Advanced cancer, Nutrition, Quality of life, Body composition,
71 Nutritional status.

72

73 **Protocol registration**

74 The research protocol was registered in PROSPERO (number: CRD42023461563).

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1. INTRODUCTION

Malnutrition is highly prevalent in those with cancer and more so in those with incurable cancer, however it remains largely unrecognised, underestimated and undertreated in clinical practice (1). The consequences of malnutrition in this population are critical with an estimated 10 – 20 % of patients with cancer dying due to the consequences of malnutrition, rather than due to the tumour itself (1). Malnutrition can have a negative impact on quality of life (QoL), anti-cancer therapy, frequency of hospital admissions and survival outcomes (2). This leads to increased distress for not only the person with cancer but also their caregivers (3).

Optimal nutritional care is becoming increasingly recognised as a critical component of modern cancer care. The European Society for Clinical Nutrition and Metabolism (ESPEN) advocate that all patients should be screened and assessed for nutritional disturbances and make recommendations specific to cancer type, treatment, and stage (4). In incurable cancer, it is agreed that optimal nutritional care has the potential to positively impact patient and caregiver distress and oncology outcomes (5-7). However, routine nutritional care that is fully integrated with oncology care remains the exception, rather than the norm.

Some studies have evaluated nutritional interventions in patients with incurable cancer, but the clinical effects have been small. This could be because the intervention has no effect however another possible explanation for the limited effectiveness of (apart from design limitations of existing work) could be that nutritional interventions have been given in isolation, for example, dietary counselling, with or without the use of oral nutritional supplements (ONS) (8-10). In oncology, it is becoming increasingly common for nutritional

120 interventions to be offered in combination with other interventions such as exercise and
121 pharmacological interventions (11, 12). However, the way in which nutritional interventions
122 are defined, delivered, received, and implemented in these trials is not uniform. In clinical
123 trials what is defined as a nutritional intervention can vary widely from nutritional counselling,
124 supplementation with micro-nutrients, ONS, enteral tube feeding and/or parenteral nutrition
125 (PN).
126
127 Ideally, optimal nutritional care should be patient-centred, tailored to their individual needs,
128 evidence-based, and delivered by an expert in nutritional therapy. Nutritional interventions
129 should be monitored, reviewed, and adjusted accordingly throughout the patient's disease
130 trajectory (4). Furthermore, those developing and delivering research trials must have a good
131 understanding of what optimal nutritional care is in oncology. Dietary counselling is the first
132 line of therapy recommended to increase oral intake to meet nutritional requirements and to
133 address any nutrition impact symptoms (NIS) (4). When nutritional requirements are unable
134 to be met through dietary strategies alone, ONS should be offered. More invasive forms
135 of nutritional therapy such as enteral tube feeding may be indicated if oral intake remains
136 poor following first-line strategies. Parenteral nutrition should only be considered if enteral
137 tube feeding is not sufficient or feasible and life expectancy is greater than three months (4).
138 To understand nutritional interventions in people with incurable cancer, whether delivered
139 in isolation or in the context of a complex intervention, a detailed examination of the
140 literature is necessary. It is important to ascertain how nutritional interventions are being
141 defined and implemented in clinical trials and whether this is reflective of what is
142 recommended in clinical practice. Other reviews have found limited evidence for nutritional
143 interventions in improving patient outcomes such as QoL, body weight and/or nutritional

144 status in those with incurable cancer and therefore a more detailed appraisal of the literature
145 is needed (13-16).
146
147 The aim of this systematic review was to describe the diversity and frequency of nutritional
148 interventions, whether given in isolation or as part of a multimodal intervention in those with
149 incurable cancer, in randomised controlled trials (RCT). The secondary aims were to describe
150 adherence and its effectiveness.
151
152 ## 2. METHODS and MATERIALS
153 Aligned with the aims, the specific research question was "Do nutritional interventions,
154 whether delivered in isolation or as part of multimodal therapy, improve primary outcomes
155 (QoL, body composition and nutritional status) and/or secondary outcomes (nutritional
156 intake, hand grip strength, fatigue, appetite and overall survival) in people with incurable
157 advanced cancer?
158
159 ### 2.1 Protocol registration
160 The research protocol was registered in PROSPERO (number: CRD42023461563). This
161 systematic review was reported in accordance with the Preferred Reporting Items for
162 Systematic Reviews and Meta-analysis (PRISMA) guidelines (17). Ethical approval was not
163 required for this systematic review.
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166

2.2 Search strategy and selection criteria

Four databases were searched electronically: Medical Literature Analysis and Retrieval System Online (MEDLINE) via Ovid, Excerpta Medica database (EMBASE) via Ovid, Cumulated Index to Nursing and Allied Health Literature (CINAHL) via EBSCO and the Cochrane Central Register of Controlled Trials (CENTRAL) with the time frame from January 2000 to 7th September 2023. This timeframe was chosen due to a lack of nutritional clinical trials before the year 2000 and to ensure studies reflected the current nutritional recommendations for those with incurable cancer. The search strategies for each database are reported in Supplementary File 1. Search results were synthesized and managed using the web-based systematic review software 'Covidence' (Veritas Health Innovations, Melbourne, Australia), and duplicates were removed (18). A consort diagram (Figure 1) as per PRISMA guidelines (19) was produced in Covidence (18). No language restrictions were set in CINAHL or CENTRAL, however only studies published in English were searched in MEDLINE and EMBASE due to the high number of search results.

2.3 Eligibility criteria

Eligible studies were those that included adult patients (≥ 18 years) with incurable cancer (defined as non-haematological malignancies, either stage IIIb or IV), with sample size ≥ 40 participants at randomisation and the intervention delivered for at least 14 days. In mixed cohort populations (curative and non-curative participants) studies were admitted if ≥75% of the population had stage IIIb-IV. They had to include a nutritional intervention which included at least one of the following: dietary counselling, ONS, enteral tube feeding and/or PN, given in isolation or as part of a multi-modal intervention. The study had to be original primary research and published in full text.

Studies were excluded if they met any of the following criteria: evaluating the effects of micronutrients, proteins, amino acids or fatty acids given in isolation; the population included patients who had completed curative treatment or were being treated with curative intent; and haematological cancers.

2.4 Selection process

All studies identified were transferred to Covidence software (18). Screening based on titles and abstracts was carried out by four independent reviewers (AM/MB/MY/BL). Full texts of potentially eligible studies were retrieved and screened by two independent reviewers. Disagreements were discussed until a consensus was reached.

2.5 Data Extraction

The data extraction was carried out independently and cross checked by three researchers (AM/MB/MY) using a data extraction template. Any anomalies were discussed amongst the researchers. Primary outcomes of interest were QoL, body composition and nutritional status. Secondary outcomes of interest were hand-grip strength (HGS), fatigue and appetite, protein and energy intake, overall survival (OS), adherence and adverse events (AE). Outcomes were based on a recent series of reviews of endpoints in cancer cachexia clinical trials (20-23). Although this study does not focus on cachexia there is an overlap between cachexia and malnutrition in advanced cancer.

2.6 Quality of studies

The quality of the included studies was assessed using the Cochrane risk of bias tool for randomised trials (RoB2) (24). This tool assesses bias that may arise at different stages of a RCT using five different domains (25). The five domains assessed were: 1. Bias arising from randomisation 2. Deviations from the intended interventions 3. Bias due to missing outcome data 4. Bias in the measurement of the outcome 5. Bias in the reporting of the selected result. Risk of bias was reported for each domain as 'low risk', 'some concerns' and 'high risk' with an overall risk of bias determined.

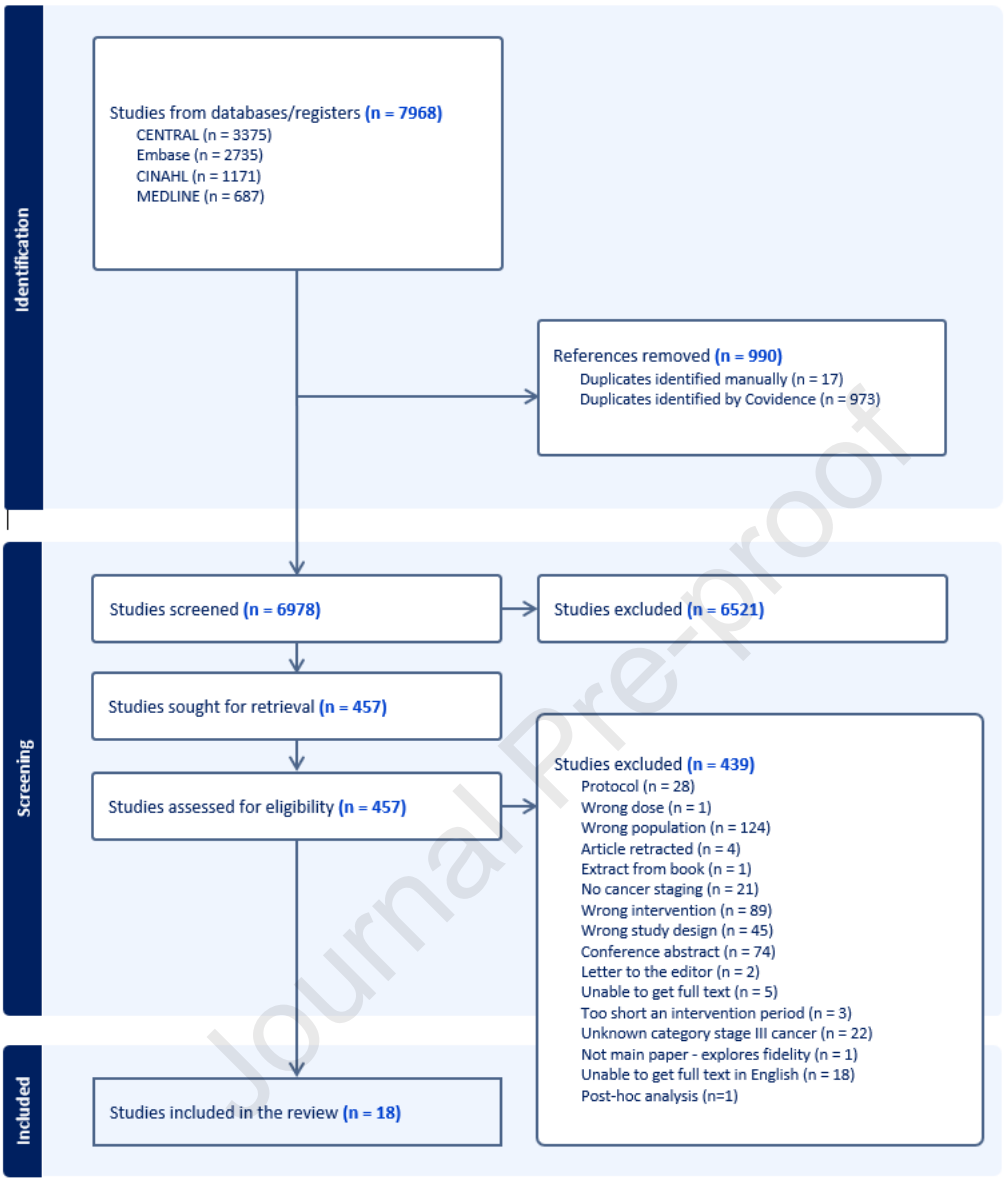
2.7 Data synthesis and analysis

Due to the diversity of the interventions in addition to the studies being heterogenous in their outcomes, the results are presented as reported in individual studies. Visualizations were conducted using RStudio Version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria), with packages including tidyverse.

3. RESULTS

Figure 1 details the PRISMA consort diagram. A total of 7968 studies were identified through the literature search. The following number of articles were retrieved from each database: 3375 (CENTRAL), 2735 (EMBASE), 1171 (CINHL) and 687 (MEDLINE). There were 990 duplicates removed and 6798 studies abstracts were screened. Resulting in 457 retained for full-text screening of which 439 were excluded for reasons listed in Figure 1. Ultimately 18

236 eligible studies were included in this review.



237

238 ***Figure 1 PRISMA consort diagram.***

239 Table 1 details the key characteristics of the eligible studies. These 18 studies included 2720
240 study participants. The median number of participants was 105 (Inter quartile range (IQR):59-
241 192) per study. The most common types of cancer were gastrointestinal (n=813), pancreatic
242 (n=491), lung (n=522) and colorectal (n=460) making up the majority of the population
243 studied. In 13 studies participants were receiving chemotherapy, targeted therapy or
244 radiotherapy (6, 8, 26-36). All studies were RCT's (6-8, 10, 12, 26-38).

245 *Table 1: Key characteristics of eligible studies*

First Author, year	Study type	Sample size	Cancer type	Cancer treatment	Intervention type	Detail of nutritional intervention	Comparison	Duration	Primary (Pre-specified) endpoint	Outcomes
Dietary counselling										
A. Molassiotis, 2021 (7)	RCT	32 Australia 42 Hong Kong	Advanced cancer – gastrointestinal & NSCLC or mesothelioma	Not stated	Nutritional - dietary counselling	Family centred nutrition intervention delivered by a dietitian. 2–3 hours of direct contact time with patients and family members over a 4–6-week period. Issues with nutrition impact symptoms and food or eating-related psychosocial concerns were addressed.	Standard care	5 weeks	Feasibility and acceptability	QoL, BW, eating-related distress, eating related enjoyment, nutritional status, energy and protein intake

A. van der Werf, 2020 (26)	RCT	107	Metastatic colorectal cancer	CAPOX, FLOFOX, capecitabine	Nutritional – dietary counselling	Individualised counselling by a dietitian at every chemotherapy cycle. Telephone consultations between each cycle. Aimed to meet protein and energy requirements. If less than 75 % of their goals were met or had significant weight loss ONS prescribed. If still unable to meet with ONS tube feeding was considered. Encouraged to perform moderate intensity physical activity for ≥30 min per /day, five days per week	Standard care – participants were referred to a dietitian when indicated	9- 19 weeks	Difference in skeletal muscle area as measured on CT scan	QoL, BW, Skeletal muscle area, HGS, PFS, OS, treatment toxicity
	Nutritional supplementation with or without dietary counselling									
C. Baldwin, 2011 (8)	RCT	358	Gastro-intestinal, NSCLC & mesothelioma	Palliative CT	Nutritional – dietary counselling, ONS	Group 2 - received advice to increase food intake by an additional 2510 kJ (600 kcal) per day. Group 3 - received one ONS (Skandishake or Calshake). Group 4- received nutritional advice to increase food intake by 250 kJ (600 kcal)/ day and one ONS. A vitamin preparation was given to groups 2, 3 and 4.	Group 1: No intervention	6 weeks.	Mortality	QoL, BW, HGS, OS

E. Cereda, 2019 (6)	RCT	166	Advanced cancer – lung, gastrointestinal, pancreas, colon, blood, breast & head & neck	Standardised CT regimens	Nutritional - dietary counselling & WPI	Dietary counselling and WPI, 2 sachets a day. WPI providing 20 g protein. ONS 1-2 cans/day were prescribed when participants were unable to meet requirements. Contact with a dietitian monthly or weekly by telephone	Dietary counselling alone. ONS 1-2 cans/day prescribed when insufficient intake. Dietitian review monthly or weekly by telephone	3 months	Change in PA at 3 months	QoL, PA, SPA, FFMI, BW, HGS, CT toxicity
K C H Fearon, 2003 (10)	RCT	200	Advanced unresectable pancreatic cancer	Not stated	Nutritional - ONS	EPA ONS containing n-3 fatty acids and antioxidants two/day in addition to normal diet	Non-EPA ONS and no antioxidants two/day in addition to normal diet	8 weeks	Body composition, dietary intake and QoL	QoL, BW, TBW, LBM, nutritional intake
A. Jatoi, 2016 (27)	RCT	118	Lung, gastrointestinal & other	Planned CT or radiotherapy	Nutritional – wine &/or ONS	White wine with ≤15 % alcohol content twice a day. Participants were also further encouraged to supplement with ONS (Boost or Ensure)	To take Boost or Ensure ONS with no alcoholic beverages	3 - 4 weeks	Appetite	QoL, BW, appetite, OS

N. Kapoor, 2017 (29)	RCT	63	Female palliative cancer cachexia. Numerous sites	Palliative CT	Dietary counselling & IAtta	Dietary counselling 30 mins, per visit and 100 g IAtta, encouragement with physical activity	Dietary counselling at every clinic visit (twice a month)	6 months	Anthropometric status, QoL	QoL, BW, MUAC, TSF, nutritional intake, nutritional status, physical activity
k. Sanchez-Lara, 2014 (30)	RCT	112	NSCLC	Paclitaxel and cisplatin carboplatin treatment.	Nutritional- ONS and standardised menus	Two EPA-ONS (Prosure) and diet based on standardised menus containing 1400, 1600, 1800, 2000 or 2200 Kcal a day. The calorie content (590 Kcals) was subtracted from the total energy requirements in intervention group, to ensure no extra calories were provided	Control group – standardised menus containing 1400, 1600, 1800, 2000 or 2200 Kcal/day	8 weeks	Body composition, nutritional intake, inflammatory parameters, QoL, CT toxicity and response, OS	QoL, BW, LBM, FM, PA, nutritional intake, CT toxicity, OS
M. Ueno, 2022 (31)	RCT	68	Advanced pancreatic cancer	Gemcitabine 1000 mg	Nutritional - ONS	EPA – ONS (Prosure) to take as a max 2/day. Gemcitabine 1,000 mg/m2 was infused on days 1, 8, and 15 every 4 weeks. If participants experienced Grade 3 diarrhoea or AE due to the EPA ONS it was reduced to one/day	gemcitabine mono-therapy	1 year	1-year survival	BW, performance status, PFS, 1-year survival, AE

	Multimodal interventions									
C. Hall, 2021 (37)	RCT	45	Gastrointestinal, thoracic, breast urological/gyn myeloma, head and neck Other: (endocrine)	Hormonal, bisphosphonate Steroids	Multimodal nutrition & exercise	Nutritional counselling by dietitian, 2 ONS/day – Prosure containing 2 g EPA. If ONS not tolerated, offered an alternative ONS & oral capsule containing 2 g EPA. Exercise aerobic (60 min/week) and resistance training 3 times/week	Standard care	9 weeks	Feasibility	Feasibility, QoL, BW, nutritional status, physical function
A. Jatoi, 2004 (28)	RCT	421	Incurable malignancies - lung, gastrointestinal & other	CT or radiotherapy was permitted	Multimodal nutrition & pharmacology	Group 1: EPA ONS 2 cans/day and a liquid placebo suspension. Group 2: MA liquid suspension 600mg/day to be taken orally with iso-caloric and isonitrogenous liquid suspension that appeared identical to the EPA ONS. Group 3: EPA ONS 2 cans/day plus MA liquid suspension 600 mg/d	N/A	4 weeks then monthly follow-up on -going until treatment stopped	10 % weight gain above baseline	QoL, BW, appetite, OS
K. Lundholm, 2004 (38)	RCT	309	Oesophageal gastric, liver, pancreatic, colorectal, lung, melanoma	Not stated	Multimodal – nutrition and pharmacology	Indomethacin (50 mg twice daily), recombinant EPO (when necessary). Nutritional support provided by the Dietitian included dietary counselling. If food intake decreased to about 90%, ONS commenced providing 450-600Kcal/day. If	Indomethacin (50 mg twice daily), recombinant EPO (when necessary). Spontaneous	Until death	Food intake, energy balance, body composition, maximum exercise capacity	Nutritional intake, energy balance, BW, LBM, body fat, TSF, HGS, maximum

						oral intake decreased to approximately 70-80% PN commenced	oral nutritional intake			exercise capacity, blood biochemistry, OS
Z. Lu, 2021, (32)	RCT	328	Gastric and oesophageal	CT- Cisplatin-based, oxaliplatin-based, paclitaxel-based, triple agents, single agents	Multi-modal nutrition & psychology	ESC nutrition & psychology. Individualised nutritional advice. Psychology assessment done individually and with family members. Psychotropic interventions were provided if necessary.	Standard oncologic care	9 weeks	OS	QoL, nutritional status, PFS, OS, tumour response
L. J. Storck, 2020 (33)	RCT	52	Metastatic or locally advanced cancer of the lungs, gastrointestinal tract, breast, ovarian, prostate, renal cell or bladder	Palliative breast and prostate cancer patients had to be under CT	Multimodal nutrition & exercise	Whey protein supplement, high in leucine. On 3 workout days, supplement was taken twice a day 20 mins before and within 2 hrs after exercise. Non-exercise days consumed one portion of the supplement in the evening. Received nutritional counselling by the dietitian.	Standard care, as per the cancer centres' standard medical therapy, following good clinical practice	3 months, 6 months for follow up	Physical function measured with SPPB	QoL, nutritional status, nutritional intake, HGS mobility, SPPB, fatigue, CRP, AE

T. S. Solheim, 2017 (34)	RCT	46	Lung & pancreatic	2 standard cycles CT	Multimodal nutrition, exercise & pharmacology	Nutritional counselling by Dietitian &/or trial nursing staff at baseline. EPA ONS (Prosure) 2/day. Exercise 30 mins aerobic exercise twice a week and resistance exercise three times a week for 20 min, devised by a physiotherapist. Participants were to take Celecoxib 300 mg once daily	Standard care. If treating clinician felt appropriate, a dietitian review was carried out.	6 weeks	Feasibility	Feasibility, BW, MM, physical activity, HGS, nutritional status, fatigue, OS, AE
A. Uster, 2018 (12)	RCT	58	Metastatic or locally advanced tumours of the gastrointestinal and lung tracts	Not stated	Multimodal nutrition & exercise	Received a minimum of three standardized nutritional counselling sessions and 60-min exercise program twice a week. ONS were given twice weekly after exercise program, containing 18-20 g protein in volumes ranging from 125 to 200 ml.	Standard care	3 months	Improvement of global health status/QoL on EORTC-QlQ-C30	QoL, BW, BIA, nutritional intake, HGS, 6 min walk test, sit to stand
	Parenteral Nutrition									
C. Bouleuc, 2020 (35)	RCT	148	Advanced cancer-digestive, pelvis, lung, prostate,	CT, hormone therapy, targeted therapy	Nutritional - PN	PN was administered via central venous route. Dosage dependent on food intake. Aim of meeting protein and energy requirements (1.2-1.5g/kg/day and 30-35	Oral feeding group were set a minimum intake of 1000	Until death	Health-related QoL deterioration-free-survival	QoL, BW, nutritional intake, PFS, OS, AE

			sarcoma, breast, melanoma, other	(ongoing and prior treatment)		kcal/kg/day respectively, not exceeding 1.25 times the resting state energy expenditure	kcal/day and 6 g nitrogen 5 days a week			
S. Obling, 2019 (36)	RCT	47	Incurable gastrointestinal cancer	Palliative CT	sHPN & dietetic counselling	sHPN group received dietetic counselling and a 24 h recall performed at each visit. PN contained 56.9 g protein, 1070 kcal/4477 kJ energy and 40 g fat per 1000 ml. Nutritional needs were estimated to be: energy 125 kJ/kg, protein 1.5 g/kg/day and fluid 35 ml/kg/day. Patients received PN at 25-35% percent of the daily nutritional need. sHPN was prescribed 2-4 days /week administered at night.	Non-sHPN - best practice nutritional care & dietary counselling, (dietetic counselling at every visit). Supplemented with ONS if energy and protein intakes insufficient. If still unable to meet requirements a feeding tube was offered	24 weeks	sHPN on FFM	QoL, FFM, HGS, six min walk test, skinfold, OS

246 *AE* adverse events, *BIA* bioelectrical impedance analysis, *BW* body weight, *CAPOX* capecitabine and oxaliplatin *CT* chemotherapy, *CRP* C-reactive protein, *EPA* eicosapentaenoic acid, *EPO* erythropoietin, *ESC* early
247 supportive care, *FFM* fat-free mass, *FFMI* fat-free mass index, *FM* fat mass, *FOLFOX* fluorouracil and oxaliplatin, *Gyn* gynaecological, *HGS* and grip strength, *LBM* lean body mass, *MA* megestrol acetate, *MM* muscle
248 mass, *MUAC* mid-upper arm circumference, *NA* non-applicable *NSCLC* non-small cell lung cancer, *OS* overall survival, *ONS* oral nutritional supplement, *PA* phase angle, *PFS* progression-free survival, *PN* parenteral
249 nutrition, *QoL* quality of life, *sHPN s*upplemented home parenteral nutrition, *SPA* standardised phase angle, *SPPB* short physical performance battery, *TBW* total body water, *TSF* triceps skinfold thickness, *WPI* whey
250 protein isolate

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260 **3.1 Characteristics of nutritional interventions tested**

261 The studies included examined the following interventions (Table 1): dietary counselling (two
262 studies) (7, 26), dietary counselling with whey protein isolate (WPI) (one study) (6) dietary
263 counselling with IAtta (one study) (29) dietary counselling and ONS (one study) (8), ONS given
264 in isolation (two studies) (10, 31) wine and ONS (one study) (27), standardised menus and
265 ONS (one study) (30) multimodal interventions (seven studies) (12, 28, 32-34, 37, 38) and PN
266 (two studies) (35, 36).

267

268 The frequency of dietary input varied among the studies and by whom this was delivered. In
269 12 of the studies, the nutritional intervention was delivered by a dietitian (6-8, 12, 26, 32-38).
270 The frequency of dietetic input ranged from weekly (6, 7, 26, 37), to six weekly (12, 32-36,
271 38). For studies that included ONS, the number prescribed ranged from one (8) to two (10,
272 28, 30, 31, 34, 37) a day.

273

274 *3.2 Dietary counselling*

275 Dietary counselling is recommended as the first-line treatment in preventing and managing
276 malnutrition and is the most commonly used approach in clinical practice (4). It aims to
277 increase nutritional intake, address (NIS) and eating-related distress (7). Two RCT's examined
278 dietary counselling (7, 26) which were both delivered by a dietitian. One of the studies (7)
279 was a family-centred nutritional intervention delivered over five weeks, this showed
280 improved Functional Assessment of Anorexia/Cachexia Therapy (FACCT) scores in the
281 intervention group compared to controls (p= 0.046). In the other study (26) participants
282 receiving chemotherapy were given dietary counselling delivered over 9-19 weeks. There

283 was no effect on QoL or skeletal muscle area between the groups. There was however a
284 positive effect on body weight (p=0.045), progression-free survival (p=0.039) and OS
285 (p=0.046) in the dietary counselling group.
286
287 *3.3 Nutritional supplementation with or without dietary counselling*
288 Oral nutritional supplements given alongside dietary counselling are also commonly used for
289 preventing and treating malnutrition, especially when nutritional needs are unable to be met
290 through diet alone (4). There were seven RCT's that evaluated nutritional supplementation
291 with or without dietary counselling. Two studies looked at ONS in isolation (10, 31) one with
292 dietary counselling and ONS (8), one with standardized menus and OS (30) one with wine
293 and ONS (27) another with dietary counselling and IAtta (29) and dietary counselling and
294 WPI (6).
295
296 *3.4 Multimodal interventions*
297 Multimodal interventions are increasingly recognised as an integral part of supportive care,
298 these can involve a combination of psychotherapy, exercise and/or pharmacology (39). For
299 the RCT's that examined multimodal interventions, they were categorised as nutrition and
300 exercise (12, 33, 37); nutrition, exercise and pharmacology (34); nutrition and psychology (32):
301 and nutrition and pharmacology (28, 38). Three of the multimodal interventions had
302 significant findings with regard to body weight (28, 34) and nutritional status (32). In the
303 study by Solheim *et al.* (34) that evaluated nutrition, exercise and pharmacology, those in the
304 treatment arm gained body weight in comparison to the control group ($p < 0.001$). Jatoi *et*
305 *al.* (28) examined nutrition and pharmacological interventions with three experimental
306 groups eicosapentaenoic acid (EPA) ONS, megestrol acetate (MA) and combined EPA ONS and

MA, they found that participants in each of the intervention groups gained > 10 % body weight (p = 0.01). In the latter two studies, participants were given an EPA ONS - 2 cans/day.

3.5 Parenteral nutrition

Parenteral nutrition is regarded as an invasive therapy and should only be considered in those with intestinal insufficiency and a life expectancy greater than three months due to increased rates of complications (4). Two RCT's (35, 36) evaluated PN taking into account participants' oral intake and PN dosage adjusted according to meet participants' nutritional requirements. One study (35) reported no difference between the groups for either QoL or weight. In contrast, Obling *et al* found QoL better ($p < 0.05$) and fat-free mass (FFM) improved ($P<0.01$) in the intervention group at 12 weeks but no significant difference at weeks 16 and 24 in FFM (36). The results are to be interpreted with caution due to the low number of participants completing the trial 36%.

3.6 Primary outcomes

Table 2 details the primary outcomes of interest, QoL, Body composition and nutritional status.

3.7 Quality of life

Quality of life was assessed in 15 studies (6-8, 10, 12, 26-30, 32, 33, 35-37). It was assessed using a variety of tools, with the most common ones being the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (40) and FAACT (41). Five studies had QoL as a primary endpoint (10, 12, 29, 30, 35) and of these, two studies had improvements (29, 30). In studies where QoL was not a primary endpoint, it

improved in two studies. One study involved dietary counselling alongside a form of psychotherapy (7), and one with PN (36). In the study by Uster *et al*. (12), QoL improved in both groups but was not statistically significant. Fearon *et al.* (10) reported no difference in QoL between the groups, however, those consuming the EPA ONS correlated positively with QoL as measured by EQ5Dindex ($r=0.37$, $p=0.01$) whereas there was no correlation in the control group ($r= 0.04$, $p= 0.77$). Kapoor et al noted significant differences in the baseline characteristics between their groups (29). Those in the intervention group had a significantly higher intake of energy and protein ($p<0.05$). They also had significantly better PG-SGA scores, Global health status scores (QoL), Fatigue scores (QoL) and appetite scores (QoL) ($p<0.05$). Those in the control group had significantly higher body fat ($p<0.05$), as reported at baseline. This may make these findings difficult to interpret.

3.8 Body composition

Body composition was reported in fifteen studies (6-8, 10, 12, 26-30, 34-38), with the majority reporting on body weight. There were significant differences in body weight in five of the studies (6, 26, 28, 30, 34) and in FFM (36, 38). Two of the studies included EPA ONS (28, 30). In the study by Sanchez *et al*. (30) the group taking the EPA ONS in addition to standardised menus maintained their weight ($p=0.01$) and increased their lean body mass (LBM) ($p=0.01$) whereas the control group lost weight and decreased their LBM, differences were significant between the groups. Jotai *et al*. (28) compared three intervention groups EPA ONS, MA and EPA ONS there was significant weight gain in each of the intervention groups: 6%, 18% and 11% ($p=0.01$) respectively. In the study by Solheim *et al*. (34) the intervention group had an increase in body weight in comparison to the control group (1.29% vs. -3.19%, $p<0.001$). In the study with dietary counselling alone (26), there was a significant positive effect on body

weight (p= 0.046). In the study looking at supplementary home parenteral nutrition (sHPN) (36), FFM was increased in the intervention group but had decreased in the non-supplemented group with the difference being significant at 12 weeks only (p<0.01). The study by Kapoor *et al*. (29), the control group had significantly decreased body weight (p=0.03), mid upper arm circumference (MUAC) (P =0.002), and body fat (p=0.02) at the end of the intervention. In the intervention group there was a trend towards weight gain (p=0.08) and significant increase in body fat (p =0.002). The study by Hall *et al*. (37) participants gained a median of 1% (IQR -3%-3%), in the control group they lost a median of 0.48% (IQR -2.6-0.64%) although this was not significant (p=0.184). In six studies there was no significant difference between the groups (8, 10, 12, 27, 35, 38).

3.9 Nutritional status

Nutritional status was reported in six studies (7, 29, 32-34, 37) the majority using the Patient-Generated Subjective Global Assessment (PG-SGA) which is a validated assessment tool. Only one study, Lu *et al*. (32) found a significant difference. The intervention group had significant improvements in the mean Nutrition Risk Score (NRS) 2002 (p <0.001) and PG-SGA (p<0.001) scores at the end of the nine-week intervention period. Kapoor *et al*. (29) reported an improvement in the intervention group but this was not statistically significant. The remaining four studies found no significant difference (7, 33, 34, 37) .

3.10 Secondary outcomes

Hand grip strength

Hand-grip strength was reported in eight studies, four of which were multimodal (12, 33, 34, 38). The remaining studies were dietary counselling (26), dietary counselling and ONS (8)

379 dietary counselling and WPI (6) and PN (36). Only one multimodal study (33) reported
380 significant findings with HGS at three months in the intervention group compared to the
381 controls from baseline (p<0.001). This was similar to findings by Cereda *et al.* (6) where there
382 was a significant difference at three months in the intervention group compared to the
383 controls (p<0.001) each of these studies included whey protein and dietary counselling.
384
385 *3.11 Nutritional intake*
386 Nutritional intake was reported in eight studies (7, 10, 12, 29, 30, 33, 36, 38) with four studies
387 showing a significant difference in either protein or energy intake or both (12, 29, 30, 38) . In
388 two of these studies (30, 38), there were significant improvements when participants
389 consumed ONS. In the study with standardised menus and EPA ONS (30), the intervention
390 group had significantly higher protein (p<0.001) and energy intakes (p <0.001) compared to
391 the controls. This is similar to findings by Fearon *et al*. (10) for those who completed the
392 eight-week intervention when looking at the combined meal intake and EPA ONS, there was
393 a significant increase in protein (p < 0.001) and energy intake (p = 0.001) in the experimental
394 group. Lundholm *et al.* (38) reported a significant difference in food intake in the intervention
395 group receiving nutritional support compared to the control group (p=0.03). It should be
396 noted that this was for carbohydrates and fats (p<0.04) but not regarding protein intake
397 (p<0.11). In the study by Uster *et al.* (12) they showed a significant difference in protein
398 intake (p=0.01) after the three-month intervention period with improved energy intakes but
399 this did not reach statistical significance (p=0.17). In the multimodal study by Storck *et al*.
400 (33) there was a trend towards an improvement in protein and energy intakes at three and
401 six months however this did not reach statistical significance.
402

403

404 *3.12 Fatigue, appetite, nausea and vomiting*

405 In four of the studies (29, 30, 33, 35) that examined fatigue in patients taking nutritional
406 interventions, there were mixed results. Two studies (29, 30) reported a difference in
407 improvements in fatigue in the intervention groups compared with the controls. In the study
408 by Kapoor *et al*. (29), participants reported a significant improvement in fatigue (p=0.002) and
409 appetite loss (p=0.006) at six months. This is similar to findings by Sanchez *et al*. (30) where
410 the intervention group reported an improvement in fatigue (p=0.05) and appetite (p=0.05)
411 and there was a significant increase in nausea and vomiting in the control group (p=0.02).
412 Uster *et al*. (12) reported less nausea and vomiting in the intervention group (p<0.01). Two
413 studies (33, 35) reported no difference in fatigue in each of the intervention and control
414 groups.

415

416 *3.13 Overall survival*

417 Overall survival was reported in twelve studies (8, 10, 26-28, 30-32, 34-36, 38) with significant
418 improvements reported in three (26, 28, 38). In one study that involved nutritional
419 counselling (26), participants in the intervention group had significantly longer progression-
420 free survival (9.6 vs. 7.6 months, p=0.039) and OS (21.7 vs. 16 months, p=0.046) in the
421 intervention and control groups respectively. In the study by Lu *et al*. (32), the median OS
422 was 14.8 months in the intervention group compared to 11.9 months in the control group
423 (p=0.021).

424 *Table 2: Summary of primary outcomes*

Outcome	Intervention	Study author	Outcome measure	Results
QoL	Dietary counselling	A. Molassiotis, 2021 (7)	FAACT	Australian intervention group FAACT QoL scale significantly improved (p=0.045) and eating related distress significantly better (p=0.046). Hong Kong intervention group patients eating related enjoyment significantly improved (p=0.024)
		A. van der Werf, 2020 (26)	EORTQ QLQ-C30	No significant difference between groups for global health score (2.2 [CI: -6.4 – 10.7], p = 0.617) and physical functioning (0.7 [CI: -7.2 – 8.6], p=0.860)
	Supplementation with or without dietary counselling	C. Baldwin, 2011 (8)	EORTC- QLQ C30 and FAACT	No significant difference between the groups (data not shown)
		E. Cereda, 2019 (6)	EORTC QLQ-C30	No significant difference between groups (2.4 [CI: -2.71 – 7.51], p=0.35)
		K C H Fearon, 2003 (10)	EORTC QLQ-C30, EQ 5D	No significant difference between the groups. There was significantly improved QoL associated to weight gain in the EPA ONS group (p <0.01)
		A. Jatoi, 2016 (27)	FAACT	No statistical differences between the groups
		N. Kapoor, 2017 (29)	EORTC-QLQ-C30	IAtta group had significant improvements in fatigue (p= 0.002) and appetite loss (p=0.006). In the control groups there was a significant decrease in global health status (p=0.018), and social functioning (p=0.004) at 6 months in each group
		K. Sanchez-Lara, 2014 (30)	EORTC-QLQ-C30 and QLQ-LC13	EPA ONS group had an increase in global health status (p= 0.02). There was significantly less fatigue (p=0.04) and anorexia (p=0.05) in EPA ONS group. The control group had a significant increase in nausea and vomiting (p=0.02) & neuropathy (p=0.004)

	Multimodal interventions	C. Hall, 2021 (37)	EORTC QLQ-C15PAL, EQ-5D	No statistical differences in trial arms. Significant differences in emotional functioning (P=0.006) for intervention group
		A. Jatoi, 2004 (28)	FAACT	Global QoL there were no significant differences (p=0.93). Improved appetite scores for MA groups compared to EPA ONS alone (p=0.004)
		Z. Lu, 2020 (32)	EORTC QLQ C30	Significant differences between groups were observed for emotional functioning (5.87 [CI: 0.05 – 11.69], p=0.048) and cognitive functioning (5.77 [CI: 0.28 – 11.25, p=0.039)
		L. J. Storck, 2020 (33)	EORTC QLQ-C30	Between groups only the dyspnoea score showed significant improvement (p=0.013, CI: -31.97 to -0.4)
		A. Uster, 2018(12)	EORTC QLQ-C30	No significant difference in QoL after 3 months. Significant difference with nausea and vomiting increasing less in the intervention group compared with controls (p <0.01)
	Parenteral nutrition	C. Bouleu, 2020 (35)	EORTC QLQ-C15-PAL,	No difference between groups for global QoL (HR: 1.31 [95% CI: 0.88–1.94], p=0.18), physical functioning (HR: 1.58 [95% CI: 1.06–2.35], p=0.024), and fatigue (HR: 1.19 [95% CI: 0.80–1.77], p=0.393). Significant increase in the pain dimension (HR: 1.79 [95% CI: 1.20–2.66], p=0.004) in the OF arm versus the PN arm
		S. Obling, 2019 (36)	EORTC QLQ-C15-PAL	Those in the sHPN had a significantly better QoL after 12 weeks (visit 3) (P <0.05)
Body composition	Dietary counselling	A. Molassiotis, 2021 (7)	BW	No significant differences found in BW between the groups (P =0.148) (Hong Kong group only)
		A. van der Werf, 2020 (26)	BW, SMA	Increase in body weight in intervention group (1.7kg [CI: 0.0 – 3.3], p=0.045). No change to SMA.

	Nutritional supplementation with or without dietary counselling	C. Baldwin, 2011 (8)	BW	No significant differences between the groups. Group randomised to receive dietary advice compared to no dietary advice were heavier at 1 year, (p=0.04) result to be interpretated with caution
		E. Cereda, 2019 (6)	BW, PA, SPA, FFMI	Treatment effect mean (95% CI) Significant difference in PhA 0.48(0.05 to 0.90) (p=0.027), SPA 0.69 (0.11 to 1.27) (p=0.021), FFMI 0.46 (0.02 to 0.90)(p=0.041), BW 1.7 (0.2 to 3.1) (p= 0.023) Significant difference in BW (1.7kg [CI: 0.2 -3.1], p=0.023), PA (0.48^{o} [CI: 0.05 – 0.9], p = 0.027), SPA (0.69^{o} [CI: 0.11-1.27], p =0.021) and FFI (0.46kg/m^{2} [CI: 0.02 – 0.9], p=0.041)
		K C H Fearon, 2003 (10)	BW, LBM	No statistically significant differences in BW (p=0.74) and LBM (p=0.88) between the groups. However, a significant attenuation of BW & LBM loss in each study group at 4 & 8 weeks (p < 0.001)
		A. Jatoi, 2016 (27)	BW	No statistically significant differences in weight stability/gain between the study arms (p = 0.98)
		N. Kapoor, 2017 (29)	BW, MUAC, body fat	Those in the control group had significantly decreased BW (p= 0.003), MUAC (p= 0.006) and body fat (p=0.032) at 6 months. Body fat significantly increased in the IAtta group (p=0.002) at the end of 6 months. Trend in BW gain in IAtta group (p=0.08).
		K.Sanchez-Lara, 2014 (30)	BW, LBM	EPA ONS group-maintained BW whereas the control group lost BW, this was significantly different between the groups at T2 (p=0.01). LBM increased in EPA ONS group and decreased in the controls. This was significant at T2 (p= 0.01)

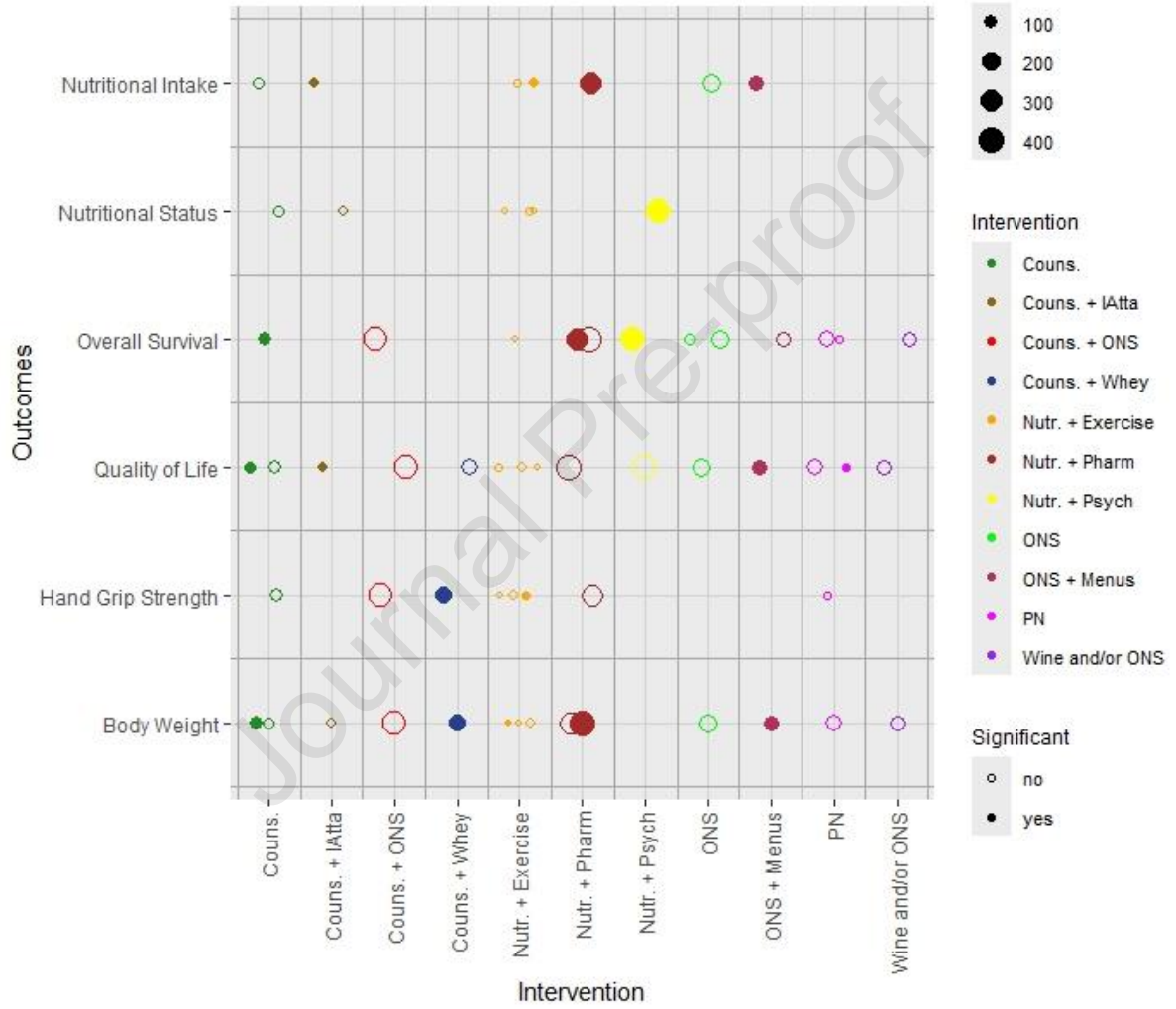
	Multimodal intervention	C. Hall, 2021 (37)	BW	BW increased by; median % change from baseline to endpoint, per trial arm (experimental 1%[IQR: -3 to 3], control -0.5% [IQR: -3 to 1],(P = 0.184)
		A. Jatoi, 2004 (28)	BW	Participants that achieved a >10 % weight gain from baseline were 6, 18, & 11 % in EPA, MA and EPA & MA groups respectively. (p=0.01)
		K. Lundholm, 2004 (38)	BW, LBM, body fat, TSF	Increased body fat in the intervention group compared to the controls (p<0.003) in as treated analysis. No difference in LBM between the groups
		T. S. Solheim, 2017 (34)	BW, MM	Participants in the treatment arm had a mean increase in BW of 1.29 % and those in the control group lost -3.19 % (p <0.001). No statistical difference in MM between the groups
		A. Uster, 2018 (12)	BW, PA	BW increased in both groups during the intervention period but not statistically significant. Insignificant changes in PA
	Parenteral nutrition	C. Bouleu, 2020 (35)	BW	No significant difference between each group
		S. Obling, 2019 (36)	FFM	Significant difference in increase in FFM between the groups (69 % & 40 % in sHPN & non-sHPN respectively) at 12 weeks (p <0.01) but not at weeks 16 or 24
Nutritional status	Dietary counselling	A. Molassiotis, 2021 (7)	PG-SGA	No significant difference in PG-SGA
	Supplementation with or without dietary counselling	N. Kapoor, 2017 (29)	PG-SGA	There was an improved score in the IAtta group but was not statistically significant. Score did not change in the control group
	Multimodal interventions	C. Hall, 2021 (37)	aPG-SGA	No significant differences found
		Z. Lu, 2020 (32)	PG-SGA, NRS 2002	Significant improvements were observed between groups for NRS 2002 (1.61 [95% CI: 1.45 - 1.78] vs. 0.73 [95% CI: 0.54 - 0.91], p<0.001) and PG-SGA (7.55 [95% CI: 6.95 - 8.15] vs. 3.40 [95% CI: 2.90 - 3.90], p<0.001).

		L. J. Storck, 2020 (33)	NRS 2002	No significant changes in NRS at 3 or 6 months between the groups
		T. S. Solheim, 2017 (34)	PG-SGA	No significant differences found

abPG-SGA abridged Patient Generated Subjective Global Assessment, *BW* body weight, ,*CI* confidence interval, *EORTC QLQ C30* European Organisation for Research and Treatment of Cancer Quality of Life, *EORTC QLQ C15* European Organisation for Research and Treatment of Cancer Quality of life Questionnaire Core 15 palliative Care, *EQ 5D* Euro Quality of Life, *EPA* eicosapentaenoic acid, *FAACT* Functional Assessment of Anorexia/Cachexia Therapy, *FFMI* fat free mass index, *HRQoL* health related quality of life, *ITT* intention to treat, *LBM* lean body mass, *MA* megestrol acetate, *MM* muscle mass, *MUAC* mid-upper arm circumference, *NRS 2002* Nutrition Risk screening, *ONS* oral nutritional supplement, *PA* phase angle, *PG-SGA* Patient Generated Subjective Global Assessment, *PN* parenteral nutrition, *QoL* quality of life, *SD* standard deviation, *sHPN* supplemented home parenteral nutrition, *SMA* skeletal muscle area, *SPA* standardised phase angle, *T0/T1/T2* timepoints, *TSF* triceps skinfold thickness, *WPI* whey protein isolate

434

435 Figure 2 shows the results on the main outcomes reported from the studies presented in a
436 balloon plot. Figure 3 details temporal trends which show an increase in studies evaluating
437 nutritional status. Overall, there has been an increase in studies examining the outcomes of
438 interest in this review.



439

440 ***Figure 2 Balloon plot of nutritional interventions and* outcomes.** *Couns* counselling, *ONS* oral nutritional supplement,
441 *Pharm* pharmacology, *PN* parenteral nutrition, *Psych* psychology. The size of the balloons is proportionate to the sample
442 size. Solid balloons show significant results.

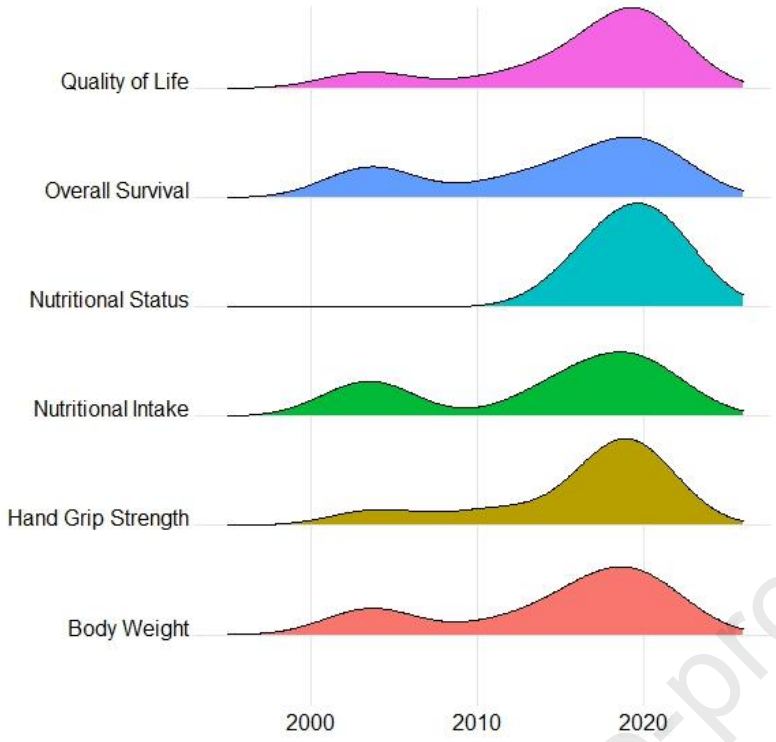


Figure 3 Temporal Trends. There has been a rise in studies reporting on nutritional status with an overall increase in studies looking at the outcomes of interest in this review.

3.14 Adherence

Of the eighteen studies, eleven reported on adherence and acceptability(6, 8, 10, 12, 27, 29-31, 33, 34, 37). Seven of these studies used ONS either given in isolation or alongside other therapies. Of these, five investigated the use of EPA ONS two cans a day (10, 30, 31, 34, 37). In two of these studies, it was reported the mean intake of the EPA ONS was 1.4 cans/day (10, 30). In the study by Sanchez-Lara *et al.* (30) more than 73% of participants assigned to the EPA-ONS group consumed the full dose of 2 cans per day (at the second timepoint) following their second cycle of chemotherapy. In two of the studies which were multimodal interventions adherence to the EPA ONS was reported as 48% in the study by Solheim *et al*. (34) and 95% in the study by Hall *et al*. (37).

458 Storck *et al*. (33) reported >70% adherence to the consumption of a leucine-rich supplement
459 and exercise. This was similar to findings by Uster *et al*. (12) where participants attended a
460 median of 75% of the training sessions and with the exception of two participants in the
461 intervention arm, they consumed at least half of the protein-rich ONS following each training
462 session. Baldwin *et al*. (8) reported decreased adherence over time in participants taking the
463 ONS which reduced to 19% by the end of the intervention period. This was similar to findings
464 in other studies using different products other than ONS (6, 27, 29). Jatoi *et al*. (27) reported
465 40% adherence with the intervention group at 3-4 weeks with wine consumption. Kapoor *et*
466 *al*. (29) where participants were asked to take 100g/day IAtta flour the mean consumption
467 for those that completed the study was 45+/- 11.26 g/day. In the study with WPI (6) where
468 participants were advised to take two sachets/day adherence was reported as 1.2 +/- 0.6
469 sachets/day (mean & SD).
470
471 *3.15 Adverse events*
472 Adverse events were reported in eight studies (6, 27, 28, 30, 31, 34, 35, 37). In the study by
473 Hall *et al*. (37) there were nine AE related to the ONS these were a range of gastrointestinal
474 symptoms, including nausea and diarrhoea. This is similar to findings reported by Ueno *et al*.
475 (31) which reported more cases of nausea 53.5%, in the EPA group compared with 30.4 % in
476 the gemcitabine group. For diarrhoea 30.2 % experienced AE in the EPA ONS group compared
477 to 17.4 % in the gemcitabine group although these results were not statistically significant.
478 In the study by Jatoi *et al*. (27) which investigated wine consumption versus ONS, there was
479 an increased number of participants reporting diarrhoea in the nutritional supplement arm.
480 In the study by Sanchez-Lara *et al*. (30) there was not an association between the
481 consumption of an EPA ONS and a significant increase in the frequency of diarrhoea (p= 0.19).

In the study by Jatoi *et al*. (28), there was a greater number of participants reporting nausea in the EPA ONS group compared to the other two intervention arms, again this did not reach statistical significance. Solheim *et al*. (34) reported similar grade 1 and 2 AE in each of the study arms, with the most common AE being nausea, pain, anorexia, constipation, dysgeusia and dyspnoea. Bouleuc *et al*. (35) reported more serious AE in the PN group compared to the controls. These were mainly concerning catheter infections. There were no gastrointestinal AE reported in the study by Creda *et al*. (6) which evaluated dietary counselling and WPI.

3.16 Quality assessment

Figure 4 shows the risk of bias for each trial. This was assessed using the Cochrane RoB2 tool (24). For sixteen studies intention to treat (ITT) figures were extracted. Per protocol figures were extracted for two of these were feasibility studies. Six of the studies were deemed overall to have a 'low risk' of bias, 10 with 'some concerns' and two a 'high risk' of bias.

Intention to treat						
Study ID	D1	D2	D3	D4	D5	Over all
Molassiotis *et al*	+	!	+	+	+	!
Van der Werf *et al*	+	!	+	+	+	!
Baldwin *et al*	+	!	!	+	+	!
Cereda et al	+	+	+	+	+	+
Fearon *et al*	+	+	+	+	+	+
Jatoi *et al* (2016)	+	!	+	+	+	!
Kapoor *et al*	!	+	!	+	+	!
Sanchez-Lara *et al*	+	+	+	+	+	+
Ueno *et al*	+	+	+	+	+	+
Jatoi *et al* (2004)	+	+	+	+	+	+
Lundholm *et al*	+	!	+	!	+	!
Lu *et al*	+	+	+	+	+	+
Storck *et al*	!	!	+	+	+	!
Uster *et al*	+	+	+	+	!	!
Bouleuc *et al*	-	!	+	+	!	-
Obling *et al*	+	!	!	+	-	-
Per- protocol						
Hall *et al*	!	!	+	+	+	!
Solheim *et al*	+	!	+	+	+	!

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

+ Low risk
! Some concerns
- High risk

Figure 4 Risk of bias assessed in each study. *This figure shows the risk of bias for each domain and the overall risk of bias. Studies were divided into ITT, 16 studies and per protocol effect, 2 studies to determine the risk of bias.*

4. DISCUSSION

4.1 Summary of Findings

This systematic review analysed 18 studies encompassing 2720 study participants. The studies evaluated various nutritional interventions, either alone or combined with other therapies. Quality of life significantly improved in four out of 15 studies. Nutritional intake significantly increased in four of the seven studies that assessed it. However, in studies where there was higher adherence to oral nutritional supplements (ONS), there was a general pattern of improved nutritional intake. There was no evidence that a higher intake of ONS resulted in a negative effect on oral intake. Yet, this can be a consequence when people are consuming ONS. Temporal trends show an increase in studies evaluating outcomes of interest in this review.

4.2 Interpretation of Findings

The findings from this systematic review have found mixed results in the outcomes of interest. This may be explained in part due to the diversity of the interventions delivered, the population studied and the heterogeneity between the studies. Those with advanced cancer, especially those diagnosed with lung, upper gastrointestinal and pancreatic which contributed to a significant number of participants included in this review are known to present with a poorer nutritional status (42). A large number of participants were also receiving chemotherapy, targeted therapy or radiotherapy which is also known to contribute to NIS which can have a detrimental effect on appetite, oral intake and nutritional status (39).

Adherence with the prescription of ONS varied amongst the studies it was reported on, with a tendency to decrease over time. In the study by Baldwin *et al*. (8) in the first week of the intervention 8% of the intervention group reported not taking any of the supplements and this increased to 48% in week 6, it should be noted this study was stopped early, following advice from the monitoring committee. It was however noted in some studies that those who adhered to the prescription of ONS had a positive effect on their nutritional intake.

In the studies which reported on AE, there was a greater number of AE recorded in the groups taking ONS, especially EPA ONS. This may have contributed to decreased adherence to the ONS. This should be considered in studies that are looking at nutritional intervention that encompasses the use of ONS, especially those containing EPA. There were marked differences in adherence in the multimodal studies by Solheim *et al*. (34) and by Hall *et al*. (37). A possible explanation could be that, in the study by Hall *et al*, participants who did not tolerate the EPA ONS were offered a substituted ONS in addition to oral EPA capsules and were also reviewed weekly by the dietitian. A subgroup analysis (31) found a significant difference between genders and the location of tumours in the consumption of ONS. For males, the average intake was 122.4 packs versus 61.5 packs of EPA ONS in females (p=0.01). Consumption in those that had pancreatic head cancer versus pancreatic body-tail cancer were 64.7 and 122.2 respectively (p=0.01).

It is paramount that when discussing and initiating nutritional interventions, especially with people with incurable cancer, preferences are considered and the impact this may have on their QoL. Failure to do so could potentially lead to poor rates of adherence. Sufficient information should be given regarding nutritional interventions to enable people to make an

informed choice, especially regarding more invasive types of nutritional therapy such as enteral tube feeding and PN.

Despite there being a sound rationale that nutritional interventions would improve outcomes in people with advanced cancer, this was not evident in the majority of studies. This may be due to the presence of cachexia or refractory cachexia which is not reversible with conventional nutritional support in isolation (43). A significant number of participants studied herein had stage IV cancer and are more likely to present with cachexia. This may explain why in some studies there was a significant improvement noted in nutritional intake but there were no significant improvements in body composition, which may conclude nutritional interventions are not effective. The interventions may however be attenuating weight loss. Dietary counselling that is individualised, tailored and monitored frequently can positively impact nutritional parameters and QoL. This may stem from the person feeling supported and having NIS addressed promptly. It can also assist with adherence to advice and nutritional interventions delivered. Studies evaluating dietary counselling and/or ONS were amongst those which reported significant differences in body composition and/or body weight. The use of EPA ONS is known to have an immune-modulating effect (44) and can help treat cachexia in the earlier stages, especially when given as part of a multimodal therapy.

For nutritional interventions to be most effective in people with advanced cancer, they need to be delivered over a substantial period of time and with on-going input. There was heterogeneity in the study's duration ranging from three weeks to one year or death. For some studies, the intervention period may not have been sufficient for significant findings.

574 There was a variable rate of attrition in the studies with some studies reporting an attrition
575 rate of 30-50% due to withdrawal, progressive disease, and death. This can also influence the
576 results due to the poor prognosis of participants, where nutritional interventions are likely to
577 be less effective due to disease progression and participants being potentially less able to
578 adhere to the intervention delivered.
579

580 *4.3 Comparison to other work in this area*

581 This review builds on previous work by Oliveira and co-workers (15), by reporting adherence
582 to nutritional interventions and adverse events (factors that will influence the efficacy of
583 interventions), and only including trials where strict criteria were met (e.g. sample size >40
584 participants, randomised trials only). Therefore, findings from the present review may allow
585 a more detailed appraisal of the nutritional interventions in this setting. There have been
586 other systematic reviews that have looked at various types of nutritional interventions, most
587 notably nutritional counselling in those with incurable cancer (13, 14, 16) with moderate
588 quality evidence. They too have not been able to reach definitive conclusions on the most
589 appropriate nutritional interventions in those with incurable cancer. Although evidence is
590 weak, there are benefits from dietary counselling delivered in isolation or in combination with
591 ONS to improve protein and energy intake and QoL as reported in some of the studies
592 included in this review. In part, this may be due to regular review and input from a dietitian
593 and nutritional advice being adjusted accordingly depending on changes to nutritional status
594 and NIS. For dietary counselling and nutritional interventions to be effective they should be
595 tailored to the individual in their unique context taking into account their cancer type, stage
596 and the presence of NIS. This should include regular review, monitoring and adapting

nutritional interventions as required. A key factor in the effectiveness of nutritional interventions is adherence and acceptability to the intervention delivered (9).

4.4 Strength and limitations

A thorough search strategy was applied that resulted in a large number of studies being retrieved and screened. For studies that included a mixed population of participants with curable and incurable cancer where staging of disease was not reported and those that contained less than 40 participants were excluded. Due to this some potentially valuable studies may not have been included in this review.

There was also heterogeneity between the studies for the nutritional interventions delivered. As the population studied here had advanced, incurable or metastatic cancer this cohort can deteriorate rapidly which can weaken the results especially where there are high attrition rates.

The nutritional risk of study participants was defined by either BMI, weight change, and/or nutritional screening scores reported at the study baseline. As some studies did not measure/report nutritional risk this, in theory, limits interpretation. However, as all studies were in patients with IIIb-IV cancers these patients were likely at nutritional risk. Accordingly, as the populations studied here had advanced, incurable or metastatic cancer, they can deteriorate rapidly and there may not have been sufficient time to see any benefit from nutritional interventions. Also, the heterogeneity of the included studies may have influenced the results as those with poorer performance status, those not deemed suitable for chemotherapy, targeted therapy or radiotherapy and those with tumours that are known to

deteriorate more quickly such as lung, gastro-intestinal and pancreatic studies, may not have had time to benefit from nutritional interventions.

4.5 Areas for Future Research

As there is an ever-increasing number of people being diagnosed with incurable cancer and are living with a live limiting illness, future studies should look to the effectiveness of earlier nutritional interventions at the point of diagnosis, regular reviews as recommended by ESPEN (4) and the impact this has on nutritional outcomes, QoL and OS. Future trials, must define and determine the stage of cachexia in trial participants and group them according to this, as this may impact the results. It is also important when interventions are delivered, they give more detail in line with the Template for Intervention Description and Replication (TIDieR) (45) checklist and standard care is clearly defined.

5. CONCLUSION

This review highlights the need for further studies looking at nutrition interventions in those with incurable cancer. Future studies should evaluate the effectiveness of earlier nutritional interventions at the point of diagnosis with regular reviews and the impact this has on nutritional outcomes, QoL, and OS. It is important when trials are being designed that they assess adherence with the nutritional interventions delivered and ways to try to mitigate poor adherence where feasible, taking into account AE and NIS. More focus should be placed on dietary counselling as a first-line therapy and ONS added where participants are unable to meet their nutritional requirements. The study populations also need to be defined more clearly with less heterogeneity. As no conclusive evidence for a single nutritional intervention

highlights the importance of individualised, tailored advice taking into account each person's unique context.

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Conflict of Interest

Professor Barry Laird has undertaken consultancy for Nutricia and Abbott. Richard Skipworth has undertaken consultancy for Actimed Therapeutics, Faraday Pharmaceuticals and Helsinn and is a member of Advisory Board for Pfizer

Author Contributions

Amy McLuskie: Conceptualization, Investigation, Methodology, Resources, Validation, Visualisation, Writing-Original Draft, Writing-review and editing. **Megan Bowers:** Investigation, Validation, Writing-review editing. **Michael Yule:** Validation, Formal analysis,

Investigation, Data curation, Writing-review editing, Visualization. **Jo Bayly:** Writing-review and editing. **Matthew Maddocks:** Conceptualization, Writing-review editing, **Marie Fallon:** Conceptualization, Writing-review editing. **Richard Skipworth:** Writing-review editing. **Barry Laird:** Conceptualization, Methodology, Validation, Investigation, Writing-review editing, Supervision.

683 ## References

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685 1. Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, et al. ESPEN
686 practical guideline: Clinical Nutrition in cancer. Clinical Nutrition. 2021;40(5):2898-913.
687 2. Cotogni P, Stragliotto S, Ossola M, Collo A, Riso S, On Behalf Of The Intersociety
688 Italian Working Group For Nutritional Support In C. The Role of Nutritional Support for
689 Cancer Patients in Palliative Care. Nutrients. 2021;13(2).
690 3. Amano K, Maeda I, Morita T, Okajima Y, Hama T, Aoyama M, et al. Eating-related
691 distress and need for nutritional support of families of advanced cancer patients: a
692 nationwide survey of bereaved family members. J Cachexia Sarcopenia Muscle.
693 2016;7(5):527-34.
694 4. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN
695 guidelines on nutrition in cancer patients. Clin Nutr. 2017;36(1):11-48.
696 5. Abbass T, Dolan RD, MacLeod N, Horgan PG, Laird BJ, McMillan DC. Comparison of
697 the prognostic value of MUST, ECOG-PS, mGPS and CT derived body composition analysis in
698 patients with advanced lung cancer. Clin Nutr ESPEN. 2020;40:349-56.
699 6. Cereda E, Turri A, Klersy C, Cappello S, Ferrari A, Filippi AR, et al. Whey protein
700 isolate supplementation improves body composition, muscle strength, and treatment
701 tolerance in malnourished advanced cancer patients undergoing chemotherapy. Cancer
702 Med. 2019;8(16):6923-32.
703 7. Molassiotis A, Brown T, Cheng HL, Byrnes A, Chan RJ, Wyld D, et al. The effects of a
704 family-centered psychosocial-based nutrition intervention in patients with advanced cancer:
705 the PiCNIC2 pilot randomised controlled trial. Nutr J. 2021;20(1):2.
706 8. Baldwin C, Spiro A, McGough C, Norman AR, Gillbanks A, Thomas K, et al. Simple
707 nutritional intervention in patients with advanced cancers of the gastrointestinal tract, non-
708 small cell lung cancers or mesothelioma and weight loss receiving chemotherapy: a
709 randomised controlled trial. J Hum Nutr Diet. 2011;24(5):431-40.
710 9. Bauer J, Capra S, Battistutta D, Davidson W, Ash S, Cancer Cachexia Study G.
711 Compliance with nutrition prescription improves outcomes in patients with unresectable
712 pancreatic cancer. Clin Nutr. 2005;24(6):998-1004.
713 10. Fearon KC, Von Meyenfeldt MF, Moses AG, Van Geenen R, Roy A, Gouma DJ, et al.
714 Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of
715 weight and lean tissue in cancer cachexia: a randomised double blind trial. Gut.
716 2003;52(10):1479-86.
717 11. Solheim TS, Laird BJA, Balstad TR, Bye A, Stene G, Baracos V, et al. Cancer cachexia:
718 rationale for the MENAC (Multimodal-Exercise, Nutrition and Anti-inflammatory medication
719 for Cachexia) trial. BMJ supportive & palliative care. 2018;8(3):258-65.
720 12. Uster A, Ruehlin M, Mey S, Gisi D, Knols R, Imoberdorf R, et al. Effects of nutrition
721 and physical exercise intervention in palliative cancer patients: A randomized controlled
722 trial. Clin Nutr. 2018;37(4):1202-9.
723 13. Blackwood HA, Hall CC, Balstad TR, Solheim TS, Fallon M, Haraldsdottir E, Laird BJ. A
724 systematic review examining nutrition support interventions in patients with incurable
725 cancer. Support Care Cancer. 2020;28(4):1877-89.

14. Balstad TR, Solheim TS, Strasser F, Kaasa S, Bye A. Dietary treatment of weight loss in patients with advanced cancer and cachexia: a systematic literature review. Crit Rev Oncol Hematol. 2014;91(2):210-21.
15. de Oliveira LC, Calixto-Lima L, Cunha GDC, Silva NFD, Souza-Silva R, Fonseca TSM, et al. Effects of specialised nutritional interventions in patients with incurable cancer: a systematic review. BMJ supportive & palliative care. 2022;12(4):388-402.
16. Ueshima J, Nagano A, Maeda K, Enomoto Y, Kumagai K, Tsutsumi R, et al. Nutritional counseling for patients with incurable cancer: Systematic review and meta-analysis. Clin Nutr. 2023;42(2):227-34.
17. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Bmj. 2009;339:b2700.
18. Covidence [Available from: https://www.covidence.org/.
19. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Rev Esp Cardiol (Engl Ed). 2021;74(9):790-9.
20. Vagnildhaug OM, Balstad TR, Ottestad I, Bye A, Greil C, Arends J, et al. Appetite and dietary intake endpoints in cancer cachexia clinical trials: Systematic Review 2 of the cachexia endpoints series. J Cachexia Sarcopenia Muscle. 2024;15(2):513-35.
21. Hjermstad MJ, Jakobsen G, Arends J, Balstad TR, Brown LR, Bye A, et al. Quality of life endpoints in cancer cachexia clinical trials: Systematic review 3 of the cachexia endpoints series. J Cachexia Sarcopenia Muscle. 2024;15(3):794-815.
22. Brown LR, Sousa MS, Yule MS, Baracos VE, McMillan DC, Arends J, et al. Body weight and composition endpoints in cancer cachexia clinical trials: Systematic Review 4 of the cachexia endpoints series. J Cachexia Sarcopenia Muscle. 2024;15(3):816-52.
23. McDonald J, Sayers J, Anker SD, Arends J, Balstad TR, Baracos V, et al. Physical function endpoints in cancer cachexia clinical trials: Systematic Review 1 of the cachexia endpoints series. J Cachexia Sarcopenia Muscle. 2023;14(5):1932-48.
24. ROB 2 A Revised Cochrane Risk of Bias Tool for randomised trials. 2019.
25. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
26. van der Werf A, Langius JAE, Beeker A, Ten Tije AJ, Vulink AJ, Haringhuizen A, et al. The effect of nutritional counseling on muscle mass and treatment outcome in patients with metastatic colorectal cancer undergoing chemotherapy: a randomized controlled trial. Clinical nutrition (Edinburgh, Scotland). 2020;39(10):3005-13.
27. Jatoi A, Qin R, Satele D, Dakhil S, Kumar P, Johnson DB, et al. "Enjoy glass of wine before eating:" a randomized trial to test the orexigenic effects of this advice in advanced cancer patients. Supportive Care in Cancer. 2016;24(9):3739-46.
28. Jatoi A, Rowland K, Loprinzi CL, Sloan JA, Dakhil SR, MacDonald N, et al. An eicosapentaenoic acid supplement versus megestrol acetate versus both for patients with cancer-associated wasting: a North Central Cancer Treatment Group and National Cancer Institute of Canada collaborative effort. Journal of clinical oncology. 2004;22(12):2469-76.
29. Kapoor N, Naufahu J, Tewfik S, Bhatnagar S, Garg R, Tewfik I. A Prospective Randomized Controlled Trial to Study the Impact of a Nutrition-Sensitive Intervention on Adult Women with Cancer Cachexia Undergoing Palliative Care in India. Integrative Cancer Therapies. 2017;16(1):74-84.

30. Sanchez-Lara K, Turcott JG, Juarez-Hernandez E, Nunez-Valencia C, Villanueva G, Guevara P, et al. Effects of an oral nutritional supplement containing eicosapentaenoic acid on nutritional and clinical outcomes in patients with advanced non-small cell lung cancer: RANDOMISED trial. Clinical Nutrition. 2014;33(6):1017-23.
31. Ueno M, Sugimori K, Taguri M, Ohkawa S, Kobayashi S, Miwa H, et al. Randomized Phase II Study of Gemcitabine Monotherapy vs. Gemcitabine with an EPA-Enriched Oral Supplement in Advanced Pancreatic Cancer. Nutrition and Cancer. 2022;74(1):122-30.
32. Lu Z, Fang Y, Liu C, Zhang X, Xin X, He Y, et al. Early Interdisciplinary Supportive Care in Patients With Previously Untreated Metastatic Esophagogastric Cancer: a Phase III Randomized Controlled Trial. Journal of clinical oncology. 2021;39(7):748-56.
33. Storck LJ, Ruehlin M, Gaeumann S, Gisi D, Schmocker M, Meffert PJ, et al. Effect of a leucine-rich supplement in combination with nutrition and physical exercise in advanced cancer patients: A randomized controlled intervention trial. Clinical nutrition (Edinburgh, Scotland). 2020;39(12):3637-44.
34. Solheim TS, Laird BJA, Balstad TR, Stene GB, Bye A, Johns N, et al. A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer. Journal of cachexia, sarcopenia and muscle. 2017;8(5):778-88.
35. Bouleuc C, Anota A, Cornet C, Grodard G, Thiery-Vuillemin A, Dubroeucq O, et al. Impact on Health-Related Quality of Life of Parenteral Nutrition for Patients with Advanced Cancer Cachexia: results from a Randomized Controlled Trial. Oncologist. 2020;25(5):e843-e51.
36. Obling SR, Wilson BV, Pfeiffer P, Kjeldsen J. Home parenteral nutrition increases fat free mass in patients with incurable gastrointestinal cancer. Results of a randomized controlled trial. Clinical nutrition (Edinburgh, Scotland). 2019;38(1):182-90.
37. Hall CC, Skipworth RJE, Blackwood H, Brown D, Cook J, Diernberger K, et al. A randomized, feasibility trial of an exercise and nutrition-based rehabilitation programme (ENeRgy) in people with cancer. J Cachexia Sarcopenia Muscle. 2021;12(6):2034-44.
38. Lundholm K, Daneryd P, Bosaeus I, Korner U, Lindholm E. Palliative nutritional intervention in addition to cyclooxygenase and erythropoietin treatment for patients with malignant disease: Effects on survival, metabolism, and function. Cancer. 2004;100(9):1967-77.
39. Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. Clinical Nutrition. 2017;36(5):1187-96.
40. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
[Available from: https://qol.eortc.org/.
41. Functional Assessment of Anorexia/Cachexia Therapy [Available from: https://www.facit.org/measures/faact.
42. Prado CM, Laviano A, Gillis C, Sung AD, Gardner M, Yalcin S, et al. Examining guidelines and new evidence in oncology nutrition: a position paper on gaps and opportunities in multimodal approaches to improve patient care. Supportive Care in Cancer. 2022;30(4):3073-83.
43. Fearon KC. Cancer cachexia: developing multimodal therapy for a multidimensional problem. Eur J Cancer. 2008;44(8):1124-32.
44. Murphy RA, Yeung E, Mazurak VC, Mourtzakis M. Influence of eicosapentaenoic acid supplementation on lean body mass in cancer cachexia. Br J Cancer. 2011;105(10):1469-73.

45. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:g1687.

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847 ***Figure 1 PRISMA consort diagram.***

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850 ***Figure 2 Balloon plot of nutritional interventions and* outcomes.** *Couns* counselling, *ONS* oral nutritional supplement,

851 *Pharm* pharmacology, *PN* parenteral nutrition, *Psych* psychology. The size of the balloons is proportionate to the sample

852 size. Solid balloons show significant result.

853

854 **Figure 3 Temporal Trends**. There has been a rise in studies reporting on nutritional status with an overall increase in studies

855 looking at the outcomes of interest in this review.

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857 **Figure 4 Risk of bias assessed in each study.** This figure shows the risk of bias for each domain and the overall risk of bias.

858 Studies were divided into ITT, 16 studies and per protocol effect, 2 studies to determine the risk of bias.

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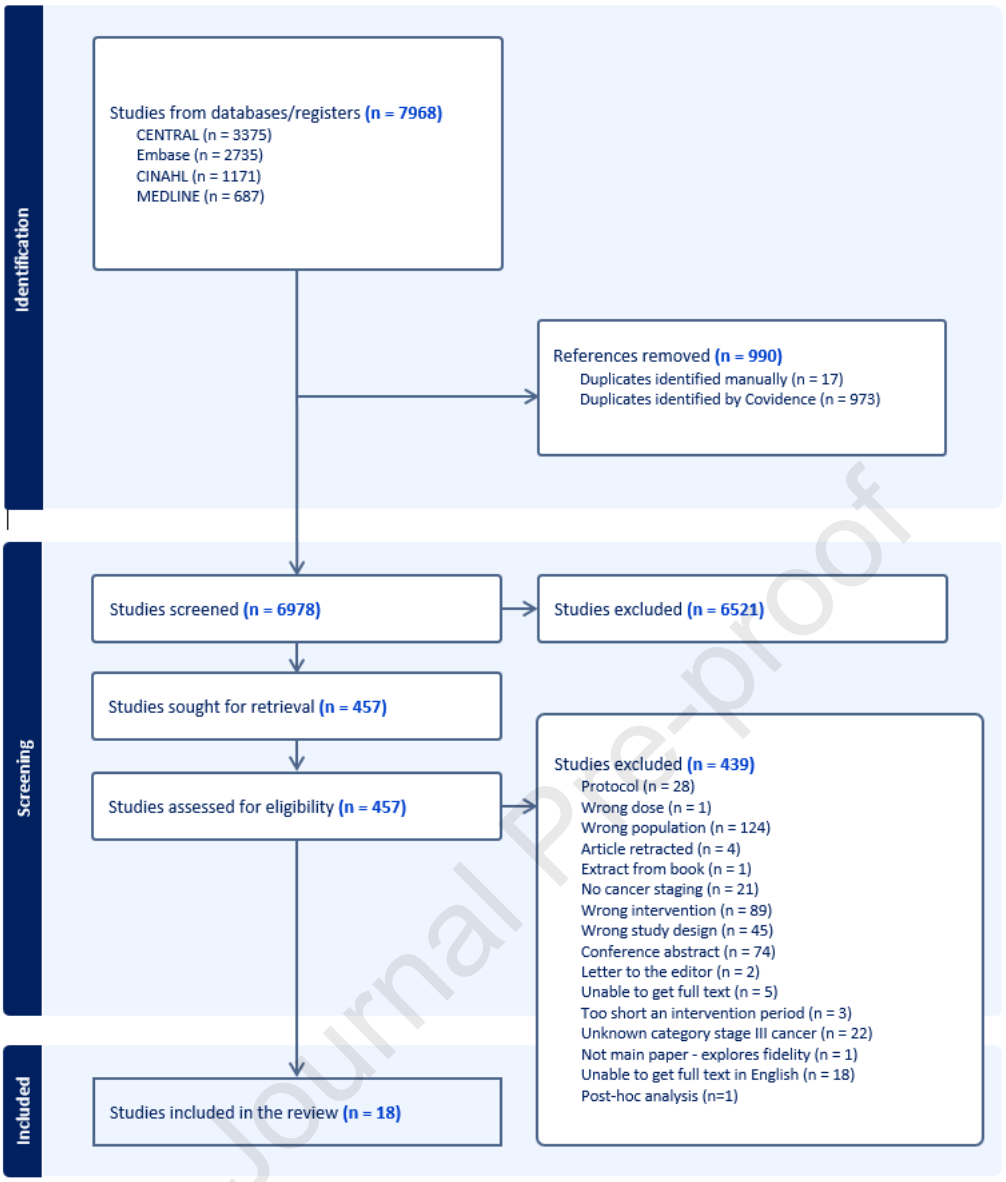

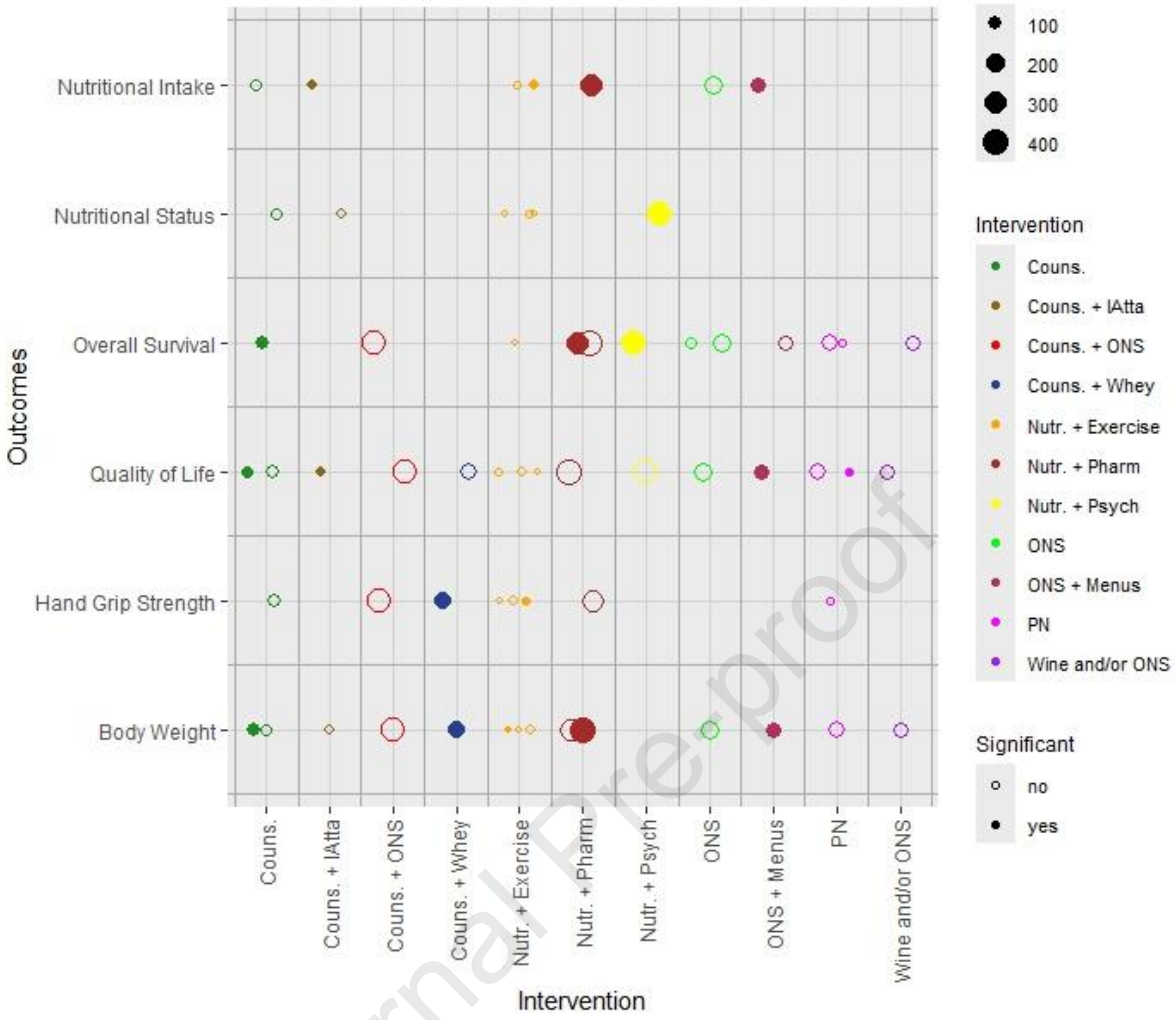

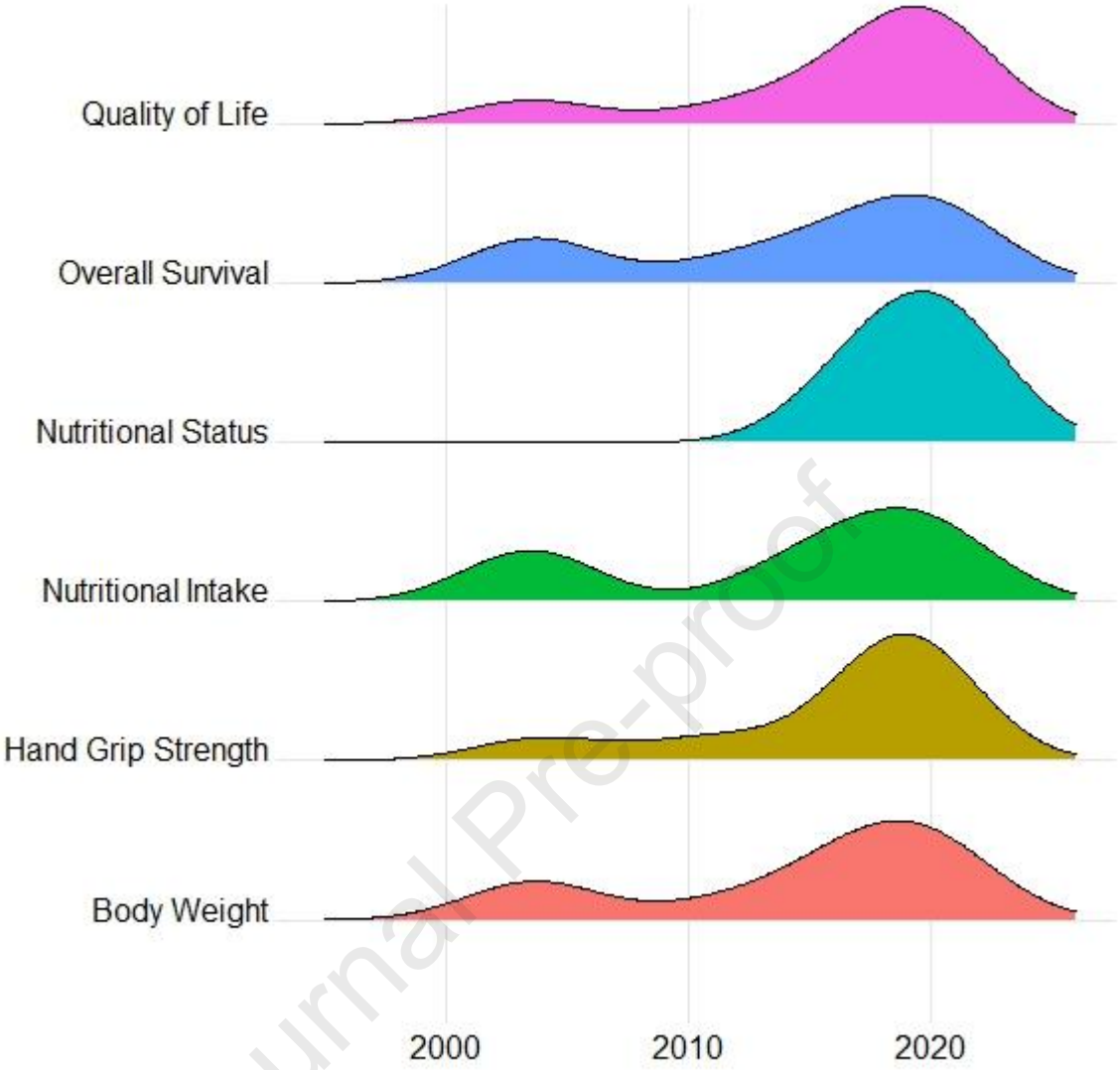

Intention to treat						
Study ID	D1	D2	D3	D4	D5	Overall
Molassiotis *et al*	+	!	+	+	+	!
Van der Werf *et al*	+	!	+	+	+	!
Baldwin *et al*	+	!	!	+	+	!
Cereda et al	+	+	+	+	+	+
Fearon *et al*	+	+	+	+	+	+
Jatoi et *al* (2016)	+	!	+	+	+	!
Kapoor *et al*	!	+	!	+	+	!
Sanchez-Lara *et al*	+	+	+	+	+	+
Ueno *et al*	+	+	+	+	+	+
Jatoi *et al* (2004)	+	+	+	+	+	+
Lundholm *et al*	+	!	+	!	+	!
Lu *et al*	+	+	+	+	+	+
Storck *et al*	!	!	+	+	+	!
Uster *et al*	+	+	+	+	!	!
Bouleuc *et al*	-	!	+	+	!	-
Obling *et al*	+	!	!	+	-	-
Per- protocol						
Hall *et al*	!	!	+	+	+	!
Solheim *et al*	+	!	+	+	+	!