Curr Oncol, Vol. 20, pp. e321-337; doi: http://dx.doi.org/10.3747/co.20.1431

REVIEW ARTICLE

Exercise and nutrition interventions in advanced lung cancer: a systematic review

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ABSTRACT

In this systematic review, we sought to evaluate the effect of physical activity or nutrition interventions (or both) in adults with advanced non-small-cell lung cancer (NSCLC).

Methods

A systematic search for relevant clinical trials was conducted in 6 electronic databases, by hand searching, and by contacting key investigators. No limits were placed on study language. Information about recruitment rates, protocol adherence, patient-reported and clinical outcome measures, and study conclusions was extracted. Methodologic quality and risk of bias in each study was assessed using validated tools.

Main Results

Six papers detailing five studies involving 203 participants met the inclusion criteria. Two of the studies were single-cohort physical activity studies (54 participants), and three were controlled nutrition studies (149 participants). All were conducted in an outpatient setting. None of the included studies combined physical activity with nutrition interventions.

Conclusions

Our systematic review suggests that exercise and nutrition interventions are not harmful and may have beneficial effects on unintentional weight loss, physical strength, and functional performance in patients with advanced NSCLC. However, the observed improvements must be interpreted with caution, because findings were not consistent across the included studies. Moreover, the included studies were small and at significant risk of bias.

More research is required to ascertain the optimal physical activity and nutrition interventions in advanced inoperable NSCLC. Specifically, the potential benefits of combining physical activity with nutrition counselling have yet to be adequately explored in this population.

KEY WORDS

Palliation, rehabilitation, systematic review, lungs, exercise, nutrition

1. BACKGROUND

Pain, fatigue, anorexia, and weight loss are some of the most prevalent physical symptoms in advanced cancers[1,2]. Unintentional weight loss is recognized as an independent predictor of poor health and earlier death in advanced cancer[3,4]. Nutrition status has also been found to directly affect both tolerance to and effectiveness of palliative chemotherapy treatments for solid tumours[3]. Although pain control in cancer is continually improving, with standardized guidance for assessment and treatment[5], the optimal management of fatigue, anorexia, and weight loss—all recognized components of cancer cachexia syndrome—are still to be determined[6,7]. Cancer cachexia syndrome is multifactorial and complex, and its causes are still not fully understood. A group of leading international experts in clinical cancer cachexia research and treatment recently defined it thus[6]:

> [A] multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Its pathophysiology is characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism. (p. 490)

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Lung cancer accounts for the highest proportion of cancer deaths in the developed world, with non-small-cell lung cancer (NSCLC) accounting for approximately 70%–85% of all lung cancer diagnoses[8–10]. The high incidence of cancer cachexia symptoms arising in advanced NSCLC[11] has made this patient population a frequent target for cancer cachexia research[12,13]. Specialized multidisciplinary clinics combining individualized nutrition and physical activity interventions, together with optimal psychosocial support and medical management, are being developed worldwide. Within these clinics, dietetic support includes advice on appropriate food selection based on likes, dislikes, and symptoms affecting dietary intake. Dietitians also advise on food fortification with or without macro- and micronutrient supplementation to correct any dietary deficiencies. Physiotherapists provide individualized exercise plans combining resistance and aerobic training for cardiovascular fitness, muscular strength, muscular endurance, flexibility, and lean mass retention. These clinics appear promising in terms of improved physical functioning, better dietary intake, weight stabilization, and fatigue reduction[14–17]. Optimal program design and timing of interventions has yet to be determined[6,18].

Our aim was to review trials of interventions in physical activity or nutrition (or both) focusing on the management of any combination of fatigue, anorexia, and unintentional weight loss (symptoms of cancer cachexia) in patients with advanced NSCLC. A further aim was to evaluate the effectiveness of the interventions.

2. METHODS

2.1 Types of Studies

Any type of clinical trial evaluating the effects of physical activity or nutrition interventions for the management of cancer cachexia symptoms in advanced NSCLC was eligible for inclusion in the review.

2.2 Types of Participants

Participants in the trials had to be adults (≥18 years of age) with stage IIIB or IV NSCLC. Participants were included regardless of whether they were actively receiving anticancer therapy at the time of the intervention.

2.3 Types of Interventions

All included papers were required to have a physical activity or nutrition treatment as the main intervention or to contain independently extractable data on such an intervention.

Physical activity interventions were defined as any one or a combination of flexibility training, resistance training, and cardiovascular training. Interventions could be supervised or unsupervised, be undertaken at any location, and be individualized or group-based in nature. Characteristics of the training program such as the type, intensity, frequency, duration, and extent of supervision and adherence are reported if that information was supplied.

Nutrition interventions included any one or a combination of the provision of dietary counselling, prescribed nutritional supplementation, and use of over-the-counter dietary supplements. Characteristics of the nutrition intervention such as the type, dose, duration, and extent of supervision and adherence are reported if that information was supplied.

2.4 Identification of Studies

A search strategy (Appendix A) was designed for identifying studies from the following databases, with no limits imposed on study language: CENTRAL (Ovid), Cochrane Database of Systematic Reviews (Ovid), MEDLINE (Ovid), EMBASE (Ovid), CINAHL Plus, and the National Research Trials Register up to October 22, 2012. Hand-searches of relevant journals were also undertaken, and the reference lists of all included studies or relevant systematic reviews were checked for further studies. Investigators known to be carrying out research in this area were also contacted for unpublished data or knowledge of the grey literature.

2.5 Data Collection and Analysis

Titles of interest were reviewed by abstract. Potentially significant papers were then obtained in full. Where the relevance of a study was unclear, a consensus was reached by the authors regarding the applicability of the participant group and reported outcome measures. Data were extracted using a pre-designed extraction form. The outcome measures of interest included patient-reported outcomes (provided using validated self-assessment tools) and clinical outcome measures. Information was also extracted on recruitment rates, attrition, adherence to the study protocol, adverse events, survival rates, and key conclusions from each study.

2.6 Assessment of Methodologic Quality of Included Reviews

Risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias for randomized controlled trials[19] and the Critical Appraisal Skills Program: Cohort Studies methodology checklist for single-cohort studies[20]. Both of those tools consider potential biases in recruitment, measurement, and reporting of study outcomes.

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3. RESULTS

3.1 Study and Patient Characteristics

Using the electronic database search strategy, we identified one hundred forty-four potential papers. The electronic database searches identified nine abstracts of interest, and a further twelve were identified by the hand searches or by contacting investigators in the field. After retrieval of twenty-one full-text articles, fifteen studies were excluded[21–35] as detailed in Figure 1. The present systematic review includes six papers detailing five studies with a total of 203 participants. The included publications relate to two single-cohort physical activity studies (54 participants) and three controlled nutrition studies (149 participants) undertaken with outpatient populations. No included study combined physical activity and nutrition interventions. Table I describes the characteristics of the included studies.

3.2 Reported Outcomes

3.2.1 Fatigue

Fatigue was a reported outcome in three of the five included studies. Using the validated outcome measurement tools Functional Assessment of Cancer Therapy–Lung[37,41] or Functional Assessment of Chronic Illness–Fatigue[37], Temel *et al.*[37] and Quist *et al.*[41] found no statistically significant changes in self-reported fatigue in participants who completed a physical activity intervention. The study by van der Meij *et al.*[39] also found no significant differences in fatigue as assessed within the European Organisation for Research and Treatment of Cancer 30-item quality-of-life questionnaire (EORTC QLQ-C30: $p = 0.57$ at week 3, $p = 0.95$ at week 5).

3.2.2 Appetite

Appetite was a reported outcome in one of the five included studies. No significant differences in appetite as assessed within the EORTC QLQ-C30 were found in the study by van der Meij[39]. Appetite was not a formal outcome in the study by Tozer *et al.*[36], but those authors reported that appetite deteriorated significantly ($p < 0.05$) in participants shortly before death.

3.2.3 Unintentional Weight Loss

Changes in total weight and lean mass were reported in three of the five included studies.

Murphy *et al.*[40] found that most participants receiving an eicosapentaenoic acid (EPA) intervention supplement gained or maintained weight and muscle, and improved the quality of their muscle through loss of intermuscular adipose tissue deposits. The improvement was significantly different ($p < 0.05$) from that in the standard-of-care control group.

Tozer *et al.*[36] found significant mean changes ($p < 0.05$) in the percentage change of body weight in an intervention group treated with cysteine-rich

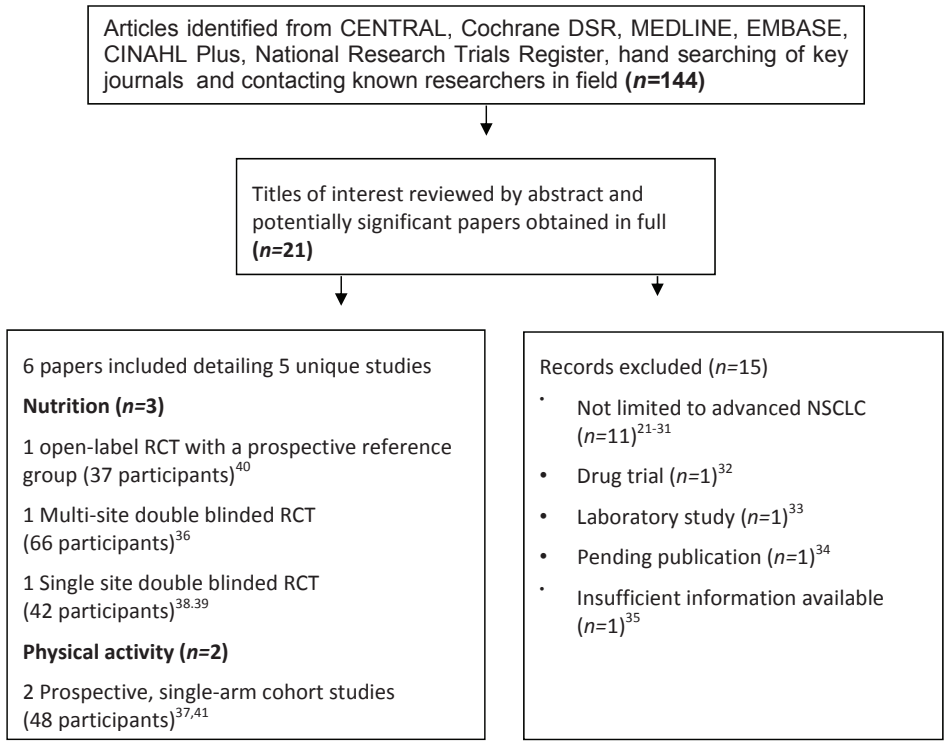

FIGURE 1 *Search strategy.*

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TABLE I Characteristics of included studies

Reference	*Study details*		
Tozer *et al.*, 2008[36]			
Study design			
Multi-site, double-blind phase II randomized controlled trial			
Start and end date			
October 2003–February 2006			
Venue			
Canadian Cancer Clinical Trial Centres			
Stated aim			
To determine if loss of body weight and body cell mass in advanced frail cancer patients with relatively poor prognosis could be ameliorated and if quality of life and functional performance could be improved with administration of high-cysteine whey-derived protein formulation compared with casein			
Study intervention details			
Participants instructed to ingest 3 scoops (3×10 g) of cysteine-rich protein daily.			
The study medication was administered in conjunction with standard of care for cancer type and stage.			
Length of intervention			
6 Months			
Control group intervention			
Casein protein in same volume and presentation			
Primary outcome measures			
Percentage change in body weight and body cell mass over 6-month period			
Secondary outcomes			
Hand grip strength			
Karnofsky performance status, McGill Quality of Life questionnaire, Edmonton Symptom Assessment System			
Mortality, biochemical markers, and disease status			
Time points for outcomes			
Baseline, week 6, month 3, and month 6			
Participants			
	Demographics	Not reported	
	Cancer type and stage	Stages IIIB and IV NSCLC	
	Cancer treatment received	Radiation or chemotherapy, or both	
	Inclusion criteria	>21 Years of age	
		Involuntary decline in body weight of >3% during 3 months immediately preceding study entry	
		Karnofsky performance status ≥ 70%	
		Life expectancy >3 months	
		Serum creatinine < 3.0 mg/dL	
		Bilirubin in the normal range	
		Alanine transaminase < 6 times upper limit of normal	
	Exclusion criteria	Pregnancy	
		History of angioedema	
		Allergy or intolerance to any agent used in study	
		Uncontrolled metastatic brain tumours	
		Ascites, edema, significant anemia	
		Currently using *N*-acetylcysteine, α-lipoic acid, or dry whey protein supplements	
		Intervention	Control
	Enrolled (*n*)	32	34
	Mean age (years)	63.6±11.4	63.8±10.1
	Sex (n women)	11	6
	Completed all assessments (*n*)	8	13

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TABLE I Continued

Reference	*Study details*
Reasons for exclusions or withdrawals	Before week 6, 17 died and 14 withdrew
	Further 8 died and 6 withdrew by 6 months
Results	
Primary outcomes	Significant increase in body cell mass compared with control group
Secondary outcome	Significant increase in handgrip strength compared with control group
Conclusions	
Key conclusions of study authors	Survival not reduced by supplementation with cysteine-rich protein compared with casein-based formula
	Intervention reversed cancer-related weight loss and loss of body cell mass significantly, with improvement in muscle force and some quality-of-life parameters, if measurements taken shortly before death were excluded
	Improvements were not replicated within control group
Other comments	Evidence limited by small number of evaluable patients
	Need to ensure that patients are not in terminal phase of illness before recruiting to this type of intervention
	22 Patients with colorectal cancer were also recruited to the study, but were not analyzed in this paper
Temel *et al.*, 2009[37]	
Study design	
Single cohort study	
Start and end date	
October 2004–August 2007	
Venue	
District general hospital outpatient setting, United States	
Stated aim	
To assess the feasibility of a structured exercise program for patients with newly diagnosed advanced NSCLC	
Study intervention details	
Treating physiotherapist undertook outcome assessments	
90–120 Minutes of moderate group-based exercise twice weekly	
10-Minute warm-up, 15 minutes treadmill, 15 minutes upright cycle	
Length of intervention	
16 Sessions over 8 weeks	
Patients could make up for missed sessions within 8-week period	
Primary outcome measures	
Feasibility	
Secondary outcomes	
6-Minute walk test, FACT-L, FACIT-Fatigue, Hospital Anxiety and Depression Scale, muscle strength	
Time points for outcomes	
Baseline and end of study (8 weeks)	
Survival data recorded until end of study (August 2007)	
Participants	
Demographics	All white
	Smoker or former smoker (n=22)
	Performance status 0 (n=10) or 1 (n=15)
Cancer type and stage	Stage IIIB NSCLC with pleural or pericardial effusions, or stage IV
Cancer treatment received	Palliative chemotherapy, radiation during or followed by chemotherapy, or radiation alone
Inclusion criteria	Within 12 weeks of diagnosis of advanced NSCLC confirmed by histology or cytology
Exclusion criteria	Unstable cardiac disease
	Baseline anemia
	Untreated bone or brain metastases preventing participation

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TABLE I Continued

Reference	*Study details*
Enrolled (*n*)	25
Mean age [(range) years]	68 (48–81)
Sex (*n* women)	16
Completed all assessments (*n*)	11
Reasons for exclusions or withdrawals	Withdrawals because of health deterioration before (*n*=5) or during study (*n*=6), travel (*n*=1), unspecified (*n*=1)
Results	
Primary outcomes	76% Completed or participated in program as long as physically able with no negative impact on fatigue or quality of life
Secondary outcome	Statistically significant improvements in the lung cancer subscale of FACT-L and in elbow extension
	No other significant findings
Conclusions	
Key conclusions of study authors	A structured, supervised exercise program may improve symptom burden and functional capacity in patients with advanced NSCLC.
	Unable to meet target recruitment rate of 30 particiants.
	Recommend increasing the accessibility of similar programs by reviewing location, duration, and intensity of physical activity
Other comments	No consideration of long-term intervention outcomes other than survival and high attrition rate
van der Meij *et al*., 2010[38] and 2012[39]	
Study design	
Double-blind randomized controlled study	
Start and end date	
March 15, 2005, to January 31, 2008	
Venue	
Amsterdam, Netherlands	
Stated aim	
To investigate the effects of an oral nutrition supplement containing omega-3 polyunsaturated fatty acids on nutrition status and inflammatory markers in patients with stage III NSCLC undergoing multimodality therapy	
Study intervention details	
Consume 2 cans daily of either a protein- and energy-dense oral nutrition supplement [480 mL ProSure (Abbott Nutrition, Maidenhead, U.K.) containing omega-3 polyunsaturated fatty acids providing 2.02 g EPA plus 0.92 g DHA daily	
Intake recorded in compliance diary	
Length of intervention	
5 Weeks alongside chemoradiotherapy treatment	
Control group intervention	
Isocaloric control oral nutritional supplement without added PUFA	
Primary outcome measures	
Body weight, body mass index, mid-arm muscle circumference, fat-free mass (bioelectrical impedance)	
Inflammatory markers	
Secondary outcomes	
Diary and plasma phospholipid concentration readings	
EORTC QLQ-C30	
Handgrip strength, physical activity (accelerometer)	
Adverse events	
Time points for outcomes	
Baseline, 3 weeks and 5 weeks	

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TABLE I Continued

Reference	*Study details*		
Participants			
Demographics	3 Patients in the intervention group and 5 in the control group were malnourished at baseline		
Cancer type and stage	Stage IIIA-N2 (n=16) or IIIB NSCLC (n=24)		
Cancer treatment received	Chemotherapy and thoracic radiotherapy		
Inclusion criteria	Stage IIIA-N2 or IIIB NSCLC		
	18–80 Years of age		
	Life expectancy >3 months		
Exclusion criteria	Surgery, chemotherapy, or radiotherapy during preceding month		
	Edema, ascites		
	Major gastrointestinal disease, chronic renal failure, uncontrolled diabetes mellitus, or HIV		
	During preceding month, using medication that could modulate metabolism or weight		
		Intervention	Control
Potential participants (n)		51	
Enrolled (n)		21	21
Completed all assessments (n)		14	19
Reasons for exclusions or withdrawals			
	Withdrew consent (n=3), disease progression (n=1), cerebrovascular accident (n=1)		
Results			
Primary outcomes	No significant differences between groups in body weight, handgrip strength, or spontaneous activity were found		
Secondary outcome	Compared with the control group, the intervention group reported significantly better quality of life and social functioning, less nausea and vomiting, fewer financial concerns (p<0.05), and better physical and cognitive function (p<0.01) on EORTC-QLQ-C30		
	No significant differences between groups in handgrip strength or spontaneous activity		
Conclusions			
Key conclusions of study authors	Study suggests beneficial effects on quality of life and spontaneous physical activity of a nutritional supplement containing EPA		
Other comments	Significant sex discrepancy between intervention and control groups		
	Compared with participants who completed the intervention, those who dropped out early had more weight loss at baseline		
	Planned recruitment numbers not achieved		
	Levels of plasma phospholipids suggestive of EPA consumption against protocol		
Murphy *et al*., 2011[40]			
Study design			
Open-label controlled study with a prospective reference group			
Start and end date			
2007–2009			
Venue			
Large medical oncology clinic, Canada			
Stated aim			
To examine the effect of a nutrition intervention with fish oil on weight and body composition against standard of care during the course of chemotherapy			
Study intervention details			
Instructed to take 2.2 g EPA daily in capsule or liquid form			
Length of intervention			
At least 6 weeks (2 cycles of chemotherapy)			

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TABLE I Continued

Reference	*Study details*		
	Control group intervention		
	Standard of care. Not placebo-controlled.		
	Primary outcome measures		
	Change in weight, skeletal muscle, adipose tissue		
	Secondary outcomes		
	Compliance, side effects		
	Time points for outcomes		
	Baseline and end of 2nd cycle of chemotherapy		
	Participants		
	Demographics	At baseline >50% of patients were overweight or obese	
	Cancer type and stage	Stage III or stage IV NSCLC	
	Cancer treatment received	Platinum-based doublet chemotherapy	
	Inclusion criteria	Clinical diagnosis of stage IIIB or IV NSCLC	
		Chemotherapy-naïve and consented to receive first-line platinum-based doublet chemotherapy	
		Able to maintain oral intake	
		ECOG performance status <2 as assessed by a physician	
	Exclusion criteria	Ineligible for chemotherapy	
		Participation in another clinical trial	
		Intervention	Control
	Screened (*n*)	204	
	Enrolled (*n*)	17	24
	Completed all assessments (*n*)	16	24
	Mean age (years)	63±2.1	64±1.8
	Sex (*n* women)	7	12
	Reasons for exclusions or withdrawals	1 Patient excluded from analysis because of poor adherence to intervention	
	Results		
	Primary outcomes	Statistically significant weight and muscle preservation compared with both comparator groups	
	Secondary outcomes	1 Patient was unable to achieve 80% compliance to the fish oil supplement and was subsequently excluded from analyses	
	Conclusions		
	Key conclusions of study authors	During first-line chemotherapy treatment, supplementation with EPA ameliorates muscle and adipose tissue wasting and improves muscle quality in advanced NSCLC compared with usual care	
	Other comments	Control arm consisted of patients opting not to receive intervention	
		Trial design chosen because of issues with compliance and contamination in similar blinded studies	
		Small number of participants were receiving potentially curative treatment, which may have biased results	
		No long-term follow-up other than survival data	
Quist *et al*., 2012[41]			
	Study design		
	Prospective, single-arm trial		
	Start and end date		
	October 2008–December 2009		
	Venue		
	Hospital- and home-based, Copenhagen, Denmark		

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TABLE I Continued

Reference	*Study details*	
	Stated aim	
	To assess if a 6-week hospital-based supervised and structured muscle–cardiovascular–relaxation training program and home-based exercise program could increase physical capacity and functional capacity in advanced lung cancer patients receiving chemotherapy	
	Study intervention details	
	Supervised group training in groups of 10–12 of 90-minute duration twice weekly:	
	• 10 minutes of cycling at 60%–90% maximal heart rate	
	• 3 sets of 5–8 repetitions of 70%–90% of 1 repetition maximum leg press, chest press, lat machine, leg extension, abdominal crunch, and lower back	
	• 10–15 minutes cardiovascular interval training on stationery bike at 85%–95% of maximum heart rate	
	• 5–10 minutes stretching large muscle groups; fortnightly program adjustment to 1 repetition maximum	
	Home based walking:	
	• 3 times per week, 20 minutes per session weeks 1 and 2, 30 minutes weeks 3 and 4, 40 minutes weeks 5 and 6	
	15–20 Minutes progressive relaxation after every exercise session	
	Length of intervention	
	6 Weeks	
	Primary outcome measures	
	Feasibility: implementation, safety, and adherence	
	Aerobic capacity, muscle strength, functional capacity, lung capacity	
	Secondary outcomes	
	Quality of life using FACT-L	
	Time points for outcomes	
	Baseline and end of 6-week intervention	
	Participants	
	Demographics	16 Retired, 11 working full- or part-time, 2 unemployed
		16 Living with a partner
		5 Smokers, 23 ex-smokers, 1 nonsmoker
		16 Low physical activity and 13 moderate to high activity before illness
	Cancer type and stage	Stage III or IV NSCLC (n=19)
		SCLC-ED (n=4)
	Cancer treatment received	Palliative chemotherapy with or without radiotherapy
	Inclusion criteria	>18 Years of age
		WHO performance status 0–2
		Stage III–IV NSCLC or SCLC-ED undergoing chemotherapy
	Exclusion criteria	Brain or bone metastases
		Prolonged bone marrow suppression
		Receiving anti-coagulant treatment
		Symptomatic heart disease
		Inability to consent
	Potential participants (n)	112
	Enrolled (n)	29
	Mean age [(range) years]	63 (45–80)
	Sex (n women)	16
	Completed all assessments (n)	23
	Reasons for exclusions or withdrawals	83 refused to participate, 3 reduced performance, 3 lost motivation
	Results	
	Primary outcomes	Exercise adherence of 73% in group training and 8.7% in home-based training for 23 who completed the 6-week program

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TABLE I Continued

Reference	*Study details*
Secondary outcome	Improvements in peak oxygen consumption, 6-minute walk test, muscle strength and emotional well-being on FACT-L (p<0.05)
	No significant improvement in overall quality of life
Conclusions	
Key conclusions of study authors	Program feasible, acceptable, safe and can improve physical and functional capacity and emotional well-being in advanced lung cancer
Other comments	Contamination with SCLC-ED patients (17% of sample)
	Only 2 patients completed home training diaries and undertook walking program (8.7% compliance)
	No consideration of long-term intervention outcomes

EPA = eicosapentaenoic acid; NSCLC = non-small-cell lung cancer; ECOG = Eastern Cooperative Oncology Group; FACT-L = Functional Assessment of Cancer Therapy–Lung; SCLC-ED = small-cell lung cancer, extensive disease; WHO = World Health Organization; DHA = docosahexaenoic acid; EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire.

protein. The control group tended to lose weight, and the active group tended to gain weight. A similar trend ($p < 0.05$) was also seen in percentage body cell mass as determined by bioelectrical impedance.

In contrast, van der Meij *et al.*[38] found no significant differences in body weight change between groups receiving an active EPA–containing intervention and a control supplement. Fat-free mass as determined by bioelectrical impedance declined in both groups, but a statistically larger loss of muscle was observed at 5 weeks in the control group ($p < 0.05$).

3.2.4 Physical Performance

Physical performance measures were reported in four of the five included studies.

Temel *et al.*[37] reported that participants who completed baseline and post-study assessments increased distance walked in 6 minutes and muscle strength, but statistical significance ($p < 0.05$) was found only for change in elbow extension, which would indicate increasing power of the triceps brachii.

In an intervention group receiving a cysteine-rich protein supplement, Tozer *et al.*[36] found a significant difference ($p < 0.05$) in hand-grip force from baseline to 6 months and at the last measurement taken more than 17 days before death. That improvement was not replicated in a group receiving a casein-based control supplement.

Quist *et al.*[41] found an increase in 6-minute walk distance and 1-repetition-maximum weight lift tests in their study completers ($p < 0.05$), indicating improvements in both exercise capacity and muscle strength.

Van der Meij *et al.*[39] found no significant differences in the physical performance of their intervention and control groups as assessed by hand-grip dynamometry and an accelerometer worn at the hip. Notably, the group receiving the intervention supplement containing EPA tended to be more physically active.

3.2.5 Quality of Life

Quality of life (QOL) was a reported outcome in three of the five included studies.

Temel *et al.*[37] and Quist *et al.*[41] reported no statistically significant changes in QOL in study participants from baseline to post-assessment. However, lung cancer symptoms significantly improved ($p < 0.05$) in the trial by Tozer *et al.*[36] over the course of the intervention, as measured by that subscale on the Functional Assessment of Cancer Therapy–Lung. Using the EORTC QLQ-C30, van der Meij *et al.*[39] reported significantly higher global QOL, better social functioning, less nausea and vomiting, fewer financial concerns ($p < 0.05$), and better physical and cognitive function ($p < 0.01$) in their intervention group than in their control group.

3.2.6 Recruitment, Attrition, and Adherence to Study Protocol

Low recruitment rates, attrition, and poor adherence to study protocol were reported as major issues in all five of the included studies (see Table I). An increase in plasma fatty acids was reported by van der Meij *et al.*[39] in some control participants, indicative of against-protocol fish-oil supplementation.

3.2.7 Adverse Events

No serious adverse events were recorded for any of the included studies. Tozer *et al.*[40] reported incidences of mild gastrointestinal symptoms thought to be related to the increased protein ingestion in both the intervention and the control group.

3.2.8 Survival

Survival was a reported outcome in two of the five included studies. The median survival of participants in the Temel *et al.*[37] study cohort was 12.98 months, which those authors deemed to be consistent with previous estimates of survival for patients with metastatic lung cancer. Tozer *et al.*[36] found a

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statistically nonsignificant, but positive trend for survival in the intervention group ($p = 0.058$), with more participants in the intervention group being alive at 6 months, an observation that they suggested might merit further study.

4. DISCUSSION

4.1 Summary of Main Results

The aim of the present paper was to review trials of physical activity or nutrition interventions (or both) focusing on the management of fatigue, anorexia, and unintentional weight loss (symptoms of cancer cachexia) in patients with advanced NSCLC, and also to evaluate the effectiveness of the interventions trialled. Despite an extensive search strategy, only six papers met the inclusion criteria. The included papers detailed five trials with 203 participants. All of the included studies had short intervention and follow-up times, except for the nutrition study undertaken by Tozer *et al.*[36]. Shorter studies benefited from reduced attrition rates, but they also prevented the drawing of any conclusions about the long-term effects of the intervention[42].

4.1.1 Physical Activity Interventions

The physical activity interventions within the present systematic review[37,41] showed that moderate-intensity physical activity interventions were not detrimental to QOL in advanced NSCLC. Also, some indications of improvement in emotional well-being[41] and lung cancer symptoms[37] were observed when participants adequately adhered to the intervention guidance.

The beneficial effects of physical activity for cancer survivors have been well established[12,43]. A recent Cochrane systematic review concluded that, compared with usual care or low-intensity activity interventions, moderate-intensity exercise may have physical, psychosocial, and spiritual benefits for cancer patients receiving cancer treatment[44].

In a cross-sectional study of patients receiving palliative care at a regional cancer centre in Canada from November 2006 to May 2007[45], higher QOL scores were self-reported by physically active patients than by those who were sedentary, even when activity levels were significantly below those recommended for the general population. Cancer patients who are more physically able are less likely to have treatment resistant-disease[46] and to experience increased life expectancy[46–48].

Findings from our systematic review add to the growing body of evidence that promotion of activity is justified, even in the late stages of NSCLC[21,49,50].

A qualitative study of 20 people with advanced NSCLC in the United States found that symptoms such as fatigue, nausea, malaise, and intolerance to cold, coupled with a lack of specific activity guidance from health care professionals and a fear of exercising unsupervised were all significant barriers to increasing or maintaining physical activity[51]. It is interesting to note that, regardless of tumour stage and functional ability, patients with advanced NSCLC have been found to be more likely to engage with and to tolerate moderate- to high-level hospital-based prescribed exercise interventions when they are referred earlier in the course of their cancer treatment[52].

4.1.2 Nutrition

The studies included in the present systematic review provided some evidence of beneficial effects from the provision of nutrition support in advanced NSCLC. The nutrition interventions used were a cysteine-rich protein supplement[36], EPA[40], and a high-protein energy-dense supplement containing omega-3 polyunsaturated fatty acids[38]. Reported benefits included maintenance of weight and muscle mass during active cancer treatment[36,53] and improvements in self-reported measures of QOL[39].

Those benefits were not routinely demonstrated across all studies. Ensuring macro- and micronutrient sufficiency is a vital component of the multimodal active management of cancer cachexia[54,55]. Although nutrition assessment and counselling are recommended for all weight-losing cancer patients[56], those approaches were absent in all of the included studies. Two of the studies used fish-oil supplementation either alone[40] or as part of a more complete nutritional supplement[38,39]. People with advanced cancer are often found to be fatty-acid-deficient, and that deficiency is strongly linked to decreased skeletal muscle mass[57]. Alterations in food preferences and dietary habits are commonly noted in advanced cancer and may exacerbate nutrient insufficiencies[54].

Obesity before diagnosis can be of prognostic advantage in advanced NSCLC[4], perhaps because of greater lean-mass stores for the body to use[56]. Weight gain through nutritional supplementation[22,58] or appetite stimulation[59] have not been shown to have similar survival benefits. A recent systematic review (13 studies with 1414 participants) compared oral-nutrition interventions against standard care for malnourished patients receiving curative or palliative treatment for any cancer diagnosis[58]. Conclusions were limited because of study heterogeneity, but the authors stated that, although oral-nutrition supplementation increased dietary intake and improved some QOL indices such as poor appetite or global QOL scores, there was no evidence that nutrition interventions alone can improve survival rates. In the absence of sufficient anabolic drive, additional energy consumed by patients with cancer cachexia syndrome appears to be preferentially stored as fat mass, increasing the metabolic demands imposed on bodily systems and worsening prognosis[3,60].

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4.2 Completeness and Applicability of Evidence

None of the included studies combined advice with respect to both nutrition management and physical activity. That observation is relevant because lean-tissue anabolism requires sufficiency in both dietary intake and contractile activity[61,62].

Recruitment into nutrition or physical activity intervention studies in advanced cancer is low and attrition is high. Withdrawal and drop-out rates often leave very small samples from which to determine any significance of findings. Study recruitment is likely to be influenced not only by the issues that affect all palliative care trials, such as participant identification and heterogeneity[63,64], but also by issues specific to exercise engagement or nutritional supplementation and palliative rehabilitation[65]. The strict criteria for entrance into trials may also be a significant bias. Often, the most unwell people are excluded from studies, making results less applicable to the population as a whole. Interventions that aim to stem weight loss often exclude those for whom the greatest weight loss has already occurred. The new definitions and staging guidance for cancer cachexia[6] have led to calls for researchers to consider more carefully suitability and optimal timing of cachexia interventions for people with cancer[18]. It is hoped that the new criteria proposed by international cancer cachexia experts[6] will better define optimal exclusion and inclusion criteria for active interventions.

Positive psychological effects have been found to occur when patients with cancer feel that something rather than nothing is being done to manage their disease[66,67], but if interventions are too burdensome, then significant attrition and poor adherence are likely. In essence, what is needed are appropriately timed, individually tailored interventions cognizant of individual's enablers and barriers to engagement[51].

4.3 Quality of the Evidence

The results of our review must be interpreted with caution because of the high risk of bias across the included studies (Table II). Studies of interventions relating to physical activity and nutrition pose many inherent risks of bias that are not easily controlled for. It is frequently impossible to blind participants to treatment intent, especially where no placebo is available or when the control intervention is standard care[63]. Advising key stakeholders and potential participants of the study hypothesis, a requirement of research ethics and governance, can also introduce bias through contamination of the control group[42,63]. The timing of research studies for cachexia symptom management has also attracted criticism, because such studies often occur during the window of expected gain from palliative anticancer therapies[68]. It is also possible that benefits observed in non-controlled studies may arise purely as a byproduct of increased monitoring and psychosocial support[69].

5. CONCLUSIONS

5.1 Implications for Practice

The present systematic review suggests that exercise and nutrition interventions are not harmful and may have beneficial effects for unintentional weight loss, physical strength, and functional performance in patients with advanced NSCLC. Such improvements must be interpreted with caution, however, because findings were not consistent across the included studies, which were small and at significant risk of bias. The lack of improvement in fatigue scores for all of the interventions is interesting. Improvements in cancer-related fatigue in advanced cancer may be masked through tiredness related to increased exertion. The masking may be particularly pronounced when the outcome measurement is taken immediately after an active physical activity intervention that lacks longer-term follow-up. Pedometers and exercise diaries might be a helpful way of demonstrating gains in function and autonomy where a level of tiredness persists[45].

5.2 Implications for Research

More research is required to ascertain optimal physical activity and nutrition interventions in advanced inoperable NSCLC. Specifically, the potential benefits of combining physical activity and nutrition counselling have yet to be adequately explored within this population. Outcome measures for assessing interventions in early-stage cancer or in cancer survivors are often inappropriate in advanced cancer, in which progressive functional decline is inevitable. It is vital that researchers separately report outcome measures in a subgroup analysis for participants with advanced illness, even if the findings are statistically nonsignificant. Adopting uniform reporting mechanisms for outcome measures of fatigue and weight loss would also provide an opportunity for meta-analyses of smaller studies[70].

6. ACKNOWLEDGMENTS

We thank the experts who responded to requests for information on their research. The research reported here was funded by the All-Ireland Institute of Hospice and Palliative Care (AIIHPC) and the HSC R&D Division, Public Health Agency, Northern Ireland. AIIHPC is an all-island organization comprising a consortium of hospices and universities, all working to improve the experience of supportive, palliative, and end-of-life care on the island of Ireland by enhancing the capacity to develop knowledge, promote

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TABLE II Risk-of-bias assessment of the included studies

Reference	*Bias type*					
	Selection	*Performance*	*Detection*	*Attrition*	*Reporting*	*Other*
Tozer *et al.*, 2008[36]	Low	Low	Low	High	High	High
Temel *et al*., 2009[37]	High	High	High	Low	Low	High
van der Meij *et al.*, 2010[38]	Low	Low	Low	Low	Low	Low to moderate
Murphy *et al.*, 2011[40]	High	High	Unclear	Low	Low	Low
Quist *et al*., 2012[41]	High	High	Unclear	Low	Low	Low

learning, influence policy, and shape practice. The aim is to secure the best care for those approaching end of life.

7. CONFLICT OF INTEREST DISCLOSURES

The authors declare that no financial conflict of interest exists.

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APPENDIX A: SEARCH STRATEGIES

OVID		*CINAHL Plus*	
Step	*Search term*	*Step*	*Search term*
1	(cachexia or cachexia anorexia syndrome or cachexia associated protein human or cachexia score or "cachexia/case reports" or "cachexia/differential diagnosis" or "cachexia/etiology" or "cachexia/metabolism").sh.	1	"Cachexia"
2	cachexia {Including Limited Related Terms}	2	(MH "Cachexia")
3	cachetic OR cachexic {Including Limited Related Terms}	3	disease-induced adj starvation
4	disease-induced adj starvation {Including Limited Related Terms}	4	disease-related adj malnutrition
5	disease-related adj malnutrition {Including Limited Related Terms}	5	cachexic or cachectic
6	wasting {Including Limited Related Terms}	6	wasting
7	(weight adj loss) OR (weight adj3 gain$) OR (weight adj3 los$) {Including Limited Related Terms}	7	(MH "Weight Loss+")
8	weight loss.sh.	8	(MH "Anorexia")
9	anorexia.sh.	9	(MH "Fatigue+") OR (MH "Cancer Fatigue")
10	fatigue.sh.	10	"tiredness"
11	fatigue {Including Limited Related Terms}	11	"fatigue"
12	weary or weariness {Including Limited Related Terms}	12	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11
13	tired or tiredness or exhaustion or asthenia {Including Limited Related Terms}	13	(MH "Carcinoma, Non-Small-Cell Lung")
14	lack or loss or lost) adj3 (energy or vigour) {Including Limited Related Terms}	14	"lung cancer"
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	15	(MH "Lung Neoplasms+")
16	lung cancer.sh.	16	S13 or S14 or S15
17	lung adj cancer {Including Limited Related Terms}	17	(MH "Nutrition+")
18	NSCLC {Including Limited Related Terms}	18	(MH "Nutritional Assessment")
19	16 or 17 or 18	19	(MH "Diet Therapy+")
20	nutrition.sh.	20	"nutrition"
21	nutrition assessment.sh.	21	(MH "Diet+")
22	nutrition therapy.sh.	22	"diet"
23	food.sh.	23	S17 or S18 or S19 or S20 or S21 or S22
24	diet$ {Including Limited Related Terms}	24	(MH "Exercise+")
25	diet {Including Limited Related Terms}	25	(MH "Physical Fitness+") OR "physical fitness" OR (MH "Physical Activity")

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OVID		*CINAHL Plus*	
Step	*Search term*	*Step*	*Search term*
26	diet.sh.	26	(MH "Sports+")
27	20 or 21 or 22 or 23 or 24 or 25 or 26	27	"sport"
28	exercise.sh.	28	"exercise training"
29	physical fitness.sh.	29	(MH "Fitness Centers")
30	sports.sh.	30	S24 or S25 or S26 or S27 or S28 or S29
31	training.sh.	31	S23 or S30
32	exercise {Including Limited Related Terms}	32	S12 and S16 and S31
33	physical adj fitness {Including Limited Related Terms}		
34	sport {Including Limited Related Terms}		
35	physical adj training {Including Limited Related Terms}		
36	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35		
41	15 and 19		
42	27 or 36		
43	41 and 42		

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