REVIEW

A Critical Review of Multimodal Interventions for Cachexia

Clare McKeaveney,[1] Peter Maxwell,[2,3] Helen Noble,[1] and Joanne Reid[1]

[1] School of Nursing and Midwifery, Medical Biology Centre, Queen's University Belfast, Belfast, Northern Ireland; [2] Centre for Public Health, Queen's University Belfast, Institute of Clinical Science, Royal Victoria Hospital, Belfast, Northern Ireland; and [3] Regional Nephrology Unit, Belfast City Hospital, Belfast Health Social Care Trust, Belfast, Northern Ireland

ABSTRACT

Currently, there are no standardized treatments for cachexia or severe wasting. There is a growing consensus advocating multimodal interventions to address the complex pathogenesis and metabolic alterations in these conditions. This review examined multimodal treatments intended to alleviate and/or stabilize cachexia and severe wasting. The objectives of this review were to *1*) identify multimodal interventions for the treatment of cachexia or associated wasting syndromes in patients with a chronic illness, *2*) assess the quality of these studies, and *3*) assess the effectiveness of multimodal interventions. Electronic databases including PubMed, MEDLINE, EMBASE, Scopus, Web of Science, Cochrane Library, CINAHL, PEDro, OpenGrey, and clinicaltrials.org were systematically searched using both text words and MeSH (medical subject heading) terms. The literature revealed a dearth of large, well-conducted trials in this area. Fourteen trials ($n = 5$ cancer, $n = 5$ chronic obstructive pulmonary disease, $n = 4$ chronic kidney disease) were included in this review. A total of 1026 patients were included across all studies; sample size ranged between 21 and 138 patients. Baseline and follow-up data were collected between 6 wk and 24 mo. All demonstrated some improvement in favor of the treatment groups, in relevant measures of body composition, nutrition, biomarkers, and functionality; however, caution should be applied due to the heterogenous nature of the interventions and small sample sizes. Overall, the evidence from this review supports the role of multimodal interventions in the treatment of severe wasting. However, randomized controlled trials with a powered sample size and sufficiently lengthy interaction period are necessary to assess if multimodal interventions are effective forms of therapy for improving body composition and nutritional and physical status in patients with cachexia and wasting. The protocol for this review is registered with Prospero (ID: CRD42019124374). *Adv Nutr* 2021;12:523–532.

Keywords: wasting, cachexia, review, interventions, multimodal

Introduction

Cachexia is a term describing a severe form of wasting. Cachexia is a complex metabolic and multifactorial syndrome requiring early intervention and multimodal management (1, 2). However, there is currently no standardized treatment for cachexia (3). It is characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) and progressive functional impairment that cannot be fully reversed by conventional nutritional support (4–6). Cachexia has a devastating physical and psychological effect on patients and caregivers (7), resulting in altered body image, reduced quality of life, and decreased physical function, and is often associated with approaching end of life. Various definitions have been proposed to define cachexia and this has evolved for disease-specific conditions such as cancer (1, 8–11). However, cachexia is reported in almost all chronic diseases at the advanced stages including cardiac disease, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis (RA), and chronic kidney disease (CKD) (12). The prevalence of cachexia varies depending on the diagnostic criteria used; 5–15% in cardiac disease (13), 5–15% in COPD (14), 15–32% in RA (15), 50–75% in CKD (16), and between 60% and 80% in cancer patients, and exceeds 80% in the last 1–2 weeks of life (12, 17).

For patients with or at risk of cachexia, a comphrensive multimodal strategy is required (18). von Haehling and colleagues highlight the urgent need to maintain body weight,

Supported by the Northern Ireland Kidney Research Fund which provided funding for the implementation, analysis, and interpretation of the data.
Supplemental Figure 1 and Supplemental Tables 1–3 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
Author disclosures: The authors report no conflicts of interest.
Address correspondence to JR (email: j.reid@qub.ac.uk).
Abbreviations used: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; FFMI, fat-free mass index; Hb, hemoglobin; HGS, handgrip strength; MA, megestrol acetate; ONS, oral nutritional supplement; PEW, protein-energy wasting; QoL, quality of life; RA, rheumatoid arthritis; RCT, randomized controlled trial; ROBINS-II, Risk of Bias in Non-randomized Studies of Interventions tool II; RT, resistance training; UWL, unintentional weight loss; 6MWT, 6-Minute Walk Test.

improve strength, enhance the capacity for independent functioning, reduce frailty, and prolong survival (12). Several potential therapeutic approaches for cachexia have been proposed on the basis of experimental studies. These include pharmacological and nonpharmacological interventions in the form of exercise and nutrition (17). These components provide an increasingly recommended framework for classification of cachexia (4) as well as a rationale for identifying multiple therapeutic targets. By combining pharmacological and nonpharmacological interventions, the multifaceted mechanisms involved in bodily wasting may be addressed simultaneously (17). However, despite growing and intensive research in the field, very little is known about effective treatment options to counteract wasting.

Research to date has predominantly focused on a wide range of single modality treatments for cachexia in various chronic illnesses including the following: pharmacological management in cancer (19), CKD (20), COPD (21), and cardiac disease (22); exercise in cancer (23), RA (24), CKD (25), and COPD (26); and nutritional interventions in cancer (27), COPD (28), and cardiac disease (29). To date, these studies have shown limited success in stabilizing or reversing wasting. Reflective of the complexity of the syndrome of cachexia, recent trials have adopted multimodal interventions (3, 30) consistent with scientific consensus, which supports combination therapy that includes exercise, nutritional support, and anti-inflammatory agents to treat the severe wasting (31). It is argued that these components may act synergistically to improve nutritional and physical status, leading to positive secondary outcomes such as improvement in quality of life (QoL) (4). However, the beneficial effects of multimodal strategies for cachexia are unknown. A critical review is required to assess current multimodal interventions in the treatment of wasting to provide an evidence base to inform future randomized controlled trials (RCTs) and inform clinical guidelines.

This review examined multimodal treatments that aim to alleviate and/or stabilize cachexia or forms of wasting. The objectives of this review included the following: *1*) identify multimodal interventions for the treatment of cachexia or associated wasting syndromes in patients with a chronic illness and *2*) assess the quality of these studies and *3*) effectiveness of multimodal interventions.

Methods

Search strategy

The protocol was registered with Prospero (ID: CRD42019124374). In consultation with a subject librarian, search terms included patient population terms (e.g., CKD, COPD, cardiac disease, immunodeficiency disorder, RA, cancer), condition terms (e.g., cachexia, cachectic), and various endpoints (e.g., weight loss, lean body mass, appetite, anorexia, fatigue, physical functioning, QoL, survival) (see **Supplemental Table 1**).

Data collection and analysis

Literature published between January 2008 and December 2019 using the databases PubMed, MEDLINE, EMBASE, Scopus, Web of Science, Cochrane Library, CINAHL, PE-Dro, OpenGrey, and ClinicalTrials.gov were systematically searched. Reference lists of included sources were also checked for relevant literature. Two review authors (JR and CM) independently assessed titles and abstracts of articles for references. Relevant data were extracted, and any disagreements were discussed and resolved by consensus with a third author (HN).

Inclusion criteria

Articles were considered eligible if they included an intervention using ≥2 modalities (e.g., pharmacological, nutritional, and/or exercise) in adults at risk of cachexia or other forms of wasting (irrespective of definition used). We included RCTs or quasi-randomized studies in a hospital setting. Studies were limited to the English language.

Exclusion criteria

Studies involving participants aged <18 years were excluded. Animal trials, conference abstracts, and case reports were not included.

Outcome measures

Endpoint measures included body weight and body composition [e.g., using BMI, bioelectrical impedance analysis, fat-free mass index (FFMI)], physiological and biochemical measures [e.g., serum concentrations of proinflammatory cytokines, hemoglobin (Hb), C-reactive protein (CRP)], functional assessments [6-Minute Walk Test (6MWT), sit-to-stand test, handgrip strength (HGS), QoL, survival], as well as feasibility outcomes (e.g., adherence to prescribed programs and occurrence of adverse events).

Quality assessment

We evaluated the quality of RCTs using the Jadad scale, which is a commonly used 3-item, 5-point quality scale, to rate independently the quality of the trials and to allocate a score of between 0 (very poor) and 5 (rigorous) (32). Domains included randomization, blinding, and withdrawals. We assessed the risk of bias for nonrandomized studies using the Risk of Bias in Non-randomized Studies of Interventions tool (ROBINS-I) (33), which considers biases from confounding factors, selection of participants, missing data, and outcomes. Two investigators (CM and JR) evaluated each study against rubrics provided by the Jadad and the ROBINS-I tool. If investigators' scores differed on a specific domain of either the Jadad or the ROBINS-I tool, they discussed to reach consensus. The Robvis tool was used to visualize risk-of-bias assessment for ROBINS-I (34). Additional quality indicators, patient characteristics, and descriptions of interventions and main outcomes are summarized in **Table 1**.

TABLE 1 Studies identified using multimodal interventions for cachexia[1]

Reference	Disease	Participants	Study type	Length of study	Definition of wasting	Intervention modality			Control (*n*)	Key findings	QA
						Exercise	Diet/ONSs	Drugs			
van Beers et al. (35)	COPD	81	RCT	12 mo	FFMI below sex and age-specific 25th percentile. FFMI values defined by Schutz et al. (36)	Adjunct exercise: cycle ergometry and treadmill walking (40 training sessions supervised 2–3/wk; plus motivational counseling in maintenance phase >4 mo)	ONS (187 kcal/125 mL; 2–3×/d, with leucine, Ω-3 PUFAs, vitamin D)	X	Placebo exercise and noncaloric cloudified aqueous solution ($n = 39$)	Treatment group reported improvements in plasma concentrations[2] and HADS.[2] EQ-5D-3L decreased in placebo group only. Both groups increased physical capacity but treatment group exceeded the minimal important difference to reduce risk of hospital admission. Trend towards weight gain in treatment group and weight loss in placebo led to between-group difference at 12 mo.[2]	3
Calder et al. (37)	COPD	68	RCT	12 wk	Precachectic (PC) and cachectic according to European Respiratory Society UWL >5% (PC) or UWL >5% with FFMI of <17 kg/m^2 (M) or 15 kg/m^2 (F)	X	200 mL/200 kcal 2×/d (10 g whey protein) and 10 μg vitamin D	2 g Ω-3 PUFAs	200 mL of milk-based comparator with no 25-hyroxyvitamin D_2, milk protein instead of pure whey protein, and sunflower oil in place of Ω-3 PUFA–containing fish ($n = 23$)	BW increase in both groups but treatment group gained more fat mass.[2] Reduced blood pressure,[2] triglycerides,[2] exercise-induced fatigue,[2] and dyspnea,[2] and increases in HDL cholesterol[2] in treatment group. Compliance and safety profile similar in both groups.	3
van Wetering et al. (38)	COPD	39	RCT	24 mo	Muscle wasting according to Vermeeren et al. (39), UWL at least 5% in 1 mo or ≥10% in 6 mo with BMI <25 kg/m^2	Exercise (cycling and walking and upper and lower strength and endurance training; home-based 30 min 2×/wk)	ONS 3× 125 mL (564 kcal) daily followed by 20 mo INS maintenance program	X	Individualized education program ($n = 16$)	Changes in favor of treatment group at 24 mo; maximum inspiration mouth pressure,[2] quadriceps average power,[2] 6MWT,[2] CET.[2] Hospital admission costs lower in treatment group.[2]	2
Pison et al. (40)	COPD	126	RCT	3 mo	Malnourished patients [BMI <21 kg/m^2 or FFMI measured by 50 kHz BIA <25th percentile of predicted, which corresponds to FFMI <18 kg/m^2 (M) or <15 kg/m^2 (F) (36, 41)]	Unsupervised cycling 3–5×/wk; elastic band exercises (3×/wk)	ONS 120 mL 3×/d	Testosterone 80 mg (M)/40 mg (F) 2×/d	"Home health education" ($n = 62$)	Improvements in treatment group for BMI,[2] FFMI,[2] Hb,[2] PW,[2] QIF,[2] ET,[2] CRQ (F only[2]). Survival was also better in compliant patients.	2

(*Continued*)

TABLE 1 (*Continued*)

Reference	Disease	Participants	Study type	Length of study	Definition of wasting	Intervention modality			Control (*n*)	Key findings	QA
						Exercise	Diet/ONSs	Drugs			
Baldi et al. (42)	COPD	28	RCT: pilot study	12 wk (within 6-mo rehab program)	Defined as dynamic weight loss (>5% BW) <6 mo	Exercise (uploaded cycling 30 min, 2×/wk)	ONS; 4 g in 200 mL, 2–3×/d	X	Exercise (uploaded cycling 30 min, 2×/wk) ($n = 14$)	Increased FFMI and BW[2] in treatment group.	0
Hristea et al. (43)	Renal	21	RCT: open-label	6 mo	PEW according to Fouque et al. (44)[3]	Intra-dialytic exercise program (cycling using cycloergometer 30 min, 3×/wk)	INS (ONS if necessary)	X	INS (ONS if necessary) ($n = 11$)	Treatment group reported improvement in 6MWT[2] and QoL. Decline in balance for control group only.	0
Jeong et al. (45)	Renal	138 Protein ($n = 45$) vs protein and exercise ($n = 49$) vs control	RCT	12 mo	Not defined	Protein and exercise group only: intra-dialysis cycling 5–45 min	Protein group/protein and exercise group: intra-dialysis ONS 30 g whey mixed with 4–6 ounces of water	X	Intra-dialysis 150 g nonnutritive beverage ($n = 44$)	Improvements for gait/leg strength for treatment groups only.	2
Dong et al. (46)	Renal	32	RCT: open label	6 mo	Not defined	RT (12 reps × 3 using leg-press machine)	Intra-dialytic ONS (480 kcal)	X	Intra-dialytic ONS (480 kcal) ($n = 17$)	BW[2] and 1-repetition maximum[2]	2
Martin-Alemañy et al. (47)	Renal	44	RCT	3 mo	PEW according to Fouque et al. (44)[3]	RT: adapted "exercise: a guide for people on dialysis" with 500-g ankle weights, medical resistance springs for hands and arms (2×/wk, 40 min, 30 reps ×4; ∼24 sessions)	ONS (434 kcal, 19.2 g protein and 22.8 g lipids)	X	ONS (434 kcal, 19.2 g protein and 22.8 g lipids) ($n = 22$)	Decrease in PEW prevalence and increases in dietary energy[2]/protein intake[2] for both groups. Increases in BW, BMI, TSF, FM percentage, HGS, phase angle, and ALB in both groups.[2]	2
Uster et al. (48)	Cancer	58	RCT	12 wk	Not defined	Group cycling, strength program, and balance training (60 min 2×/wk)	INS plus supplement	X	Controls to keep "everyday habits without chasing daily PA level. ONS provided when medically indicated by treating physician" ($n = 29$)	Improvements in treatment group for nausea/vomiting (patient-rated symptom scale) and protein intake[2]	2
Solheim et al. (49)	Cancer	46	RCT: feasibility	6 wk	Cachexia: BMI <30 kg/m^2 and 20% weight loss <6 mo	Aerobic 30 min, 2×/wk; resistance training 20 min, 3×/wk (home-based)	ONS (542 kcal; 30 g protein)	Ibuprofen 1200 mg/d; Ω-3 PUFAs (2 g EPA/1 g DHA)	"No nutrition, exercise or NSAIDs offered" ($n = 21$)	Attrition rate 11% (41/46). Good feasibility and safety profile. BW gain in treatment group and BW loss in control group.	2
Xu et al. (50)	Cancer	59	RCT: pilot study	6 wk	Not defined	Supervised walking 3×/wk (protocol provided)	INS vs feeding tube	X	"Conventional medical care" ($n = 28$)	Lower intravenous nutritional need, wheelchair use, less decline in 6MWT[2] (100-m), HGS[2] (3 kg), and BW[2] (2 kg) in treatment group.	2

(*Continued*)

TABLE 1 (*Continued*)

Reference	Disease	Participants	Study type	Length of study	Definition of wasting	Intervention modality			Control (*n*)	Key findings	QA
						Exercise	Diet/ONSs	Drugs			
Wen et al. (51)	Cancer	102	RCT	8 wk	Loss of >5% of pre-illness or ideal BMI in previous 3 mo	X	MA 160 mg po, 2×/d	Thalidomide (50 mg po, 2×/d)	MA 160 mg po, 2×/d ($n = 54$)	Treatment group reported improvements in GPS and BW,[2] QoL,[2] appetite,[2] HGS,[2] fatigue,[2] ECOG PS,[2] IL-6,[2] TNF.[2] Controls also reported improvements in BW[2] and appetite.[2]	2
Schink et al. (52)	Cancer	131	Controlled pilot study	12 wk	Not defined	WB-EMS 20 min, 2×/wk	INS	X	INS ($n = 35$)	Treatment group improved PF[2] and PS[2] only	Low

[1]ALB, serum albumin; BIA, bioelectrical impedance analysis; BMI, body mass index; BW, body weight; CET, cycle endurance test; COPD, chronic obstructive pulmonary disease; CRQ, chronic respiratory disease questionnaire; DHA, docosahexaenoic acid; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EQ-5D-3L, EuroQoL Five Dimensions Questionnaire; EPA, eicosapentaenoic acid; ET, endurance time; FFMI, fat-free mass index; FM, fat mass; F, female; GPS, Glasgow Prognostic Score; HADS, Hospital Anxiety and Depression Scale; Hb, haemoglobin; HDL, high-density lipoprotein; HGS, handgrip strength; IL-6, Interleukin-6; INS, individualized nutritional support; M, male; MA, megestrol acetate; MIN, minutes; NSAIDs, nonsteroidal anti-inflammatory drugs; ONS, oral nutritional supplement; PA, physical activity; PEW, protein-energy wasting; PF, physical functioning; PS, performance status; PW, peak workload; QA, quality assessment; QlF, quadriceps isometric force; QoL, quality of Life; RCT, randomized controlled trial; RT, resistance training; TNF, tumor necrosis factor; TSF, tricep skinfold thickness; UWL, unintentional weight loss; WB-EMS, whole-body electro-myostimulation; 6MWT, 6-Minute Walk Test; Ω-3 PUFAs, omega-3 polyunsaturated fatty acids.

[2]$P < 0.05$ is considered significant.

[3]Three of 4 of the following listed categories and at least 1 test of the following—*1*) albumin: <3.8 g/100 mL; *2*) BMI <23 kg/m^2; UWL over time: 5% over 3 mo or 10% over 6 mo or total body fat percentage <10%; *3*) muscle mass: reduced muscle mass 5% over 3 mo or 10% over 6 mo or reduced mid-arm circumference area or creatinine appearance; and *4*) dietary intake: unintentional low dietary energy intake <1 g/(kg of ideal weight/d) for at least 2 mo, unintentional low dietary energy intake <30 kcal/(kg of ideal weight/d) for at least 2 mo.

Results

In total, 12,153 articles were collated from 7 databases (see **Supplemental Figure 1**). Findings were screened for duplicates and 2428 were subsequently removed. Initial screening of title and abstract removed 9545 articles, 180 of which were selected for full screening analysis. This review identified 14 studies that implemented a multimodal intervention for severe wasting. A total of 1026 patients were included across all studies; sample sizes ranged between 21 and 138 patients. Baseline and follow-up data were collected between 6 wk and 24 mo.

Study design comprised 2 double-blind studies, 6 unspecified RCTs, 2 pilot RCTs, 2 open-label RCTs, an RCT feasibility study, and a controlled pilot study. The mean Jadad score was 2 (range: 0–3), implying inconsistent quality of design and inadequate randomization and blinding. ROBIN-I score was used for the only nonrandomized study (52) and considered at low risk of bias. The majority of studies focused on interventions aimed at patients with cancer ($n = 5$), followed by COPD ($n = 5$), then CKD ($n = 4$). The following synthesis presents results based on disease assessing the following aspects: operational definition applied, type of interventions, endpoints, adherence and adverse outcomes, study limitations, and quality assessment.

COPD ($n = 5$)

Five multimodal intervention RCT studies were conducted in patients with COPD. An operational definition for wasting was provided for all studies; however, these varied. Pison et al. (40), Calder et al. (37), and van Beers et al. (35) referred to standardized indices of FFMI [e.g., age and sex specific below the 25th percentile of FFMI; i.e., <17 kg/m^2 (males), <15 kg/m^2 (females)]. However, variations exist within these, including Calder et al. (37) who distinguishes between pre-cachexia [unintentional weight loss (UWL) >5%] and overt cachexia (>5% with respective FFMI) according to the European Respiratory Society. In addition, Pison et al. (40) references FFMI or BMI (in kg/m^2) <21, whereas van Wetering et al. (38) suggest that a UWL of 5% over 1 mo or 10% over 6 mo with a BMI <25 were appropriate cutoffs for wasting. Baldi et al. (42) refers only to weight loss as >5% over 6 mo.

Four of the 5 studies included some form of exercise (e.g., cycling, walking and/or resistance bands and/or weight training), but all studies included an oral nutritional supplement (ONS) (35, 37, 38, 40, 42). Branded (35, 38, 40, 42) and an unbranded (37) compound(s) were prescribed in similar quantities. In addition, nutritional counselling was included during the maintenance phase of 2 studies (35, 38). All studies included assessments of body composition reporting on weight, BMI, and fat mass as well as tests of physical function (e.g., 6MWT, cycle endurance test). Additional measures included metabolic biomarkers and inflammatory markers (40, 37), QoL (38, 35), and survival (40). All studies that implemented an exercise regimen and ONS reported significant improvements in favor of the treatment groups; however, after 24 mo, improvements in primary endpoints

such as BMI and FFMI were lost in van Wetering et al. (38). However, caution is needed in interpretation due to the small sample size, which reduces generalizability. Other limitations were noted, including an overrepresentation of females, indicating a randomization bias and a lack of blinding (42). The majority of the studies were not double-blinded due to the nature of the interventions, which makes double blinding impractical. However, 2 studies were double blinded (35, 37) and 2 studies were single blinded (38, 40).

Pison et al. (40) included the largest sample and was also the only study to include all 3 recommended components: exercise, ONS, and pharmacology (testosterone). Of note, the exercise regimen was not supervised; however, significant improvement in clinical outcomes as well as survival suggest efficacy of a home-based intervention. Calder et al. (37) was the only other study to include a drug component (Ω-3 PUFAs) in combination with an ONS. Despite reported weight gain in both groups, Calder et al. (37) reported several positive effects for the treatment group, including improved body composition (e.g., fat mass), functionality (e.g., fatigue, dyspnea), and metabolic biomarkers (e.g., blood pressure, lipoprotein, and cholesterol). Control groups in 2 studies (35, 37) replicated placebo conditions appropriately. For example, van Beers et al. (35) implemented a placebo exercise and noncaloric cloudified aqueous solution. Pison et al. (40) and van Wetering et al. (38) used education programs as control conditions. Baldi et al. (42) provided both groups with the same exercise intervention with the adjunct of ONS only for the intervention.

Studies that included interventions with no exercise component (37) had lower drop-out rates (9%). van Wetering et al. (38) demonstrated the poorest adherence (31% dropout) but this may not be surprising after 2 y. In addition, after 15 mo, van Beers et al. (35) experienced a similar adherence (25% dropout). Dropout was high, resulting in 21% of patients dropping out or failing to adhere at 6 mo follow-up (40). Conversely, Baldi et al. (42) described that 14% of the patients had some difficulties in adhering to the home-based nutritional rehabilitation.

CKD ($n = 4$)

Two of the 4 multimodal interventions for CKD did not define criteria for severe wasting (45, 46). The remaining 2 studies used protein-energy wasting (PEW) according to the Fouque et al. (44) definition; however, minor differences were described (43, 47), and Martin-Alemañy et al. (47) do not mention reduction in dietary intake as an optional criterion. All interventions were conducted intra-dialysis, which involved cycling (43, 45) or resistance training (RT) (46, 47). Three studies also included an ONS also while on dialysis (43, 45, 46). However, Hristea et al. (43) included dietary counseling. The nutritional supplements for these trials also constituted respective control components.

Hristea et al. (43) provided the most comprehensive assessments, including weight change (e.g., BMI), biomarkers (e.g., serum albumin), physical function (e.g., 6MWT), and nutrition (e.g., dietary energy intake). Jeong et al. (45) assessed body composition, physical function, and muscle strength. However, Dong et al. (46) did not include an assessment of functionality and Martin-Alemañy et al. (47) did not include nutritional parameters. Both studies using RT failed to report significant improvements (46, 47). Jeong et al. (45) also found no significant change in the primary outcome of physical function or body composition, but there were modest improvements as interventions increased (protein-only to protein and exercise), suggesting more comprehensive lifestyle modifications are needed in this population. Safety profile was also regarded as good, with 1 adverse event reported by Jeong et al. (45) within the protein-only group. Hristea et al. (43) also reported positive benefits, such as improvement in QoL and physical function, but no evidence of PEW remission.

Cancer ($n = 5$)

Five multimodal interventions were reported for patients with cancer and severe wasting. Three studies failed to provide inclusion criteria for patients at risk of severe wasting (48, 50, 52). Only 1 study defined cachexia, Solheim et al. (49) cites weight loss and BMI cutoff (<30). Wen et al. (51) referred to involuntary weight loss of >5% with different trajectories of 3 mo. Endpoints were less varied between cancer studies. Uster et al. (48), Wen et al. (51), Solheim et al. (49), and Schink et al. (52) assessed a variety of similar parameters, including biomarkers (e.g., Hb, CRP), nutrition (e.g., dietary intake), body composition (e.g., body weight), and functionality (e.g., QoL, fatigue). Xu et al. (50) focused on body composition as well as adherence. However, comparison between multimodal interventions was not possible as each implemented different modalities.

Solheim et al. (49) used 3 components, including aerobic training and RT, ONS, and ibuprofen. No significant changes were reported, and survival was similar between groups compared with usual care. However, the primary endpoint was feasibility, which demonstrated no serious adverse events and good compliance. Of note, Solheim et al. (49) used an open-label design trial, which may have compliance issues given the impact of knowledge of treatment allocation. Uster et al. (48) also failed to show an improvement in overall QoL through the implementation of a combined nutritional support and physical exercise program (cycling and balance training). Adherence was good (67%), and significant improvement in dietary intake and the reduction in nausea and vomiting was found. This helps to demonstrate the potential that multimodal therapy holds for cancer cachexia. However, limitations for outcome measures, such as bioimpedance analysis and QoL, were considered problematic.

Improvements were reported by Xu et al. (50) in those who received the supervised walking program and nutritional advice. Walking distance, HGS, and body weight improved significantly compared with controls. Compliance was moderately high at 68%. However, the authors noted this was a powered, but small sample. In addition, there was an overrepresentation of males and 1 ethnic group. There is also a need for longer follow-up observations. Wen et al.

(51) also reported significant improvements in body weight, appetite, QoL, HGS, fatigue, and metabolic biomarkers (e.g., Glasgow Prognostic Score, IL-6, TNF). Patients who received megestrol acetate (MA) and thalidomide experienced greater improvements compared with controls who only received MA. Despite this, controls also experienced significant improvements in body weight and appetite, suggesting MA also has beneficial effects. In addition, the safety profile was reported as good, with a low occurrence rate of toxicities for both groups. Schink et al. (52) also reported significant improvements in body composition and physical function but no significant changes in QoL, fatigue, or biochemistry. Schink et al. (52) provided a unique intervention using strength training in the form of whole-body electro-myostimulation with nutritional support in cancer patients. This pilot study reported a combined approach was effective; however, the comparison, using dietary therapy alone, also showed improvements in physical function (e.g., HGS).

Quality of the evidence

The only 2 double-blind RCTs, according to the Jadad scale (see **Supplemental Table 2**), were deemed as having moderate quality (a score of 3) (35, 37). Although randomization and attrition were adequately described, the blinding procedures were not provided. In addition, both studies were reported as inadequately powered. Two studies reported a score of zero using the Jadad assessment tool (42, 43). Randomization procedures were not described, and blinding was absent. Other issues included small sample sizes, low adherence, and high dropout. The majority of randomized studies ($n = 9$) had a score of 2, suggesting low quality (38, 40, 45–51). Randomization procedures tended to be provided, but these studies failed to include information on any blinding. The majority of studies were not powered by study completion or did not describe a power calculation at the outset of the study (35, 38, 40, 45, 47, 49). Xu et al. (50) reported sufficient power to assess some, not all, measures with confidence. Wen et al. (51), Dong et al. (46), and Uster et al. (48) also reported powered samples at 90%, 90%, and 80%, respectively. In addition, although all studies provided detailed drop-out and withdrawal rates, these tended to be considerable from the initially small sample sizes. The only nonrandomized study by Schink et al. (52) was reported as having a low risk of bias using ROBINS-I quality assessment (see **Supplemental Table 3**). Information related to selection biases (e.g., selection of participants) and confounding factors was not described; however, appropriate detail was provided for issues relating to the intervention, missing data, and reported outcomes.

Discussion

This review identified 13 RCTs and 1 feasibility trial delivering multimodal interventions to patients at risk or requiring treatment for wasting. The trials demonstrated mixed evidence regarding the benefits of interventions; however, heterogeneity of intervention components and small sample sizes need to be taken into consideration. These studies reflect a growing scientific consensus recommending a framework of combined pharmacological, nutritional, and exercise components to treat cachexia and wasting conditions in chronic disease (4). This review highlights greater improved endpoints when combining treatment modalities, furthering our understanding of the effectiveness of multimodal interventions in cachexia. Furthermore, the majority of studies found significant improvements in weight gain, body composition, and physical activity as well as functionality (37, 38, 40, 42, 50, 51). However, some studies failed to find clinically significant improvements (43). Various limitations were identified, including small sample sizes (42), short follow-up periods (49, 50), high drop-out rates, lack of appropriate controls or assessment procedures (45), and modest intervention regimens (46). Overall, the nature of studies included were heterogeneous (e.g., dose, modality, disease). Larger and longer trials are required to clarify whether multimodal interventions are effective forms of therapy for improving body composition and nutritional and physical status in patients with wasting and advanced disease.

Single therapies such as pharmacological or nonpharmacological, nutritional interventions, or physical exercise programs demonstrate variable results across different diseases (4). Trials of nutritional support and other single-component interventions have proven unsuccessful in stopping or reversing cachectic deterioration (1). It is evident that multimodal intervention strategies (i.e., forms of resistance exercise, nutritional supplementation and/or drugs) aimed at muscle mass, physical function, nutritional status, and clinical outcome in patients at risk of or requiring treatment for cachexia are necessary. Multimodal interventions are likely to provide comprehensive lifestyle modifications to patient cohorts at high risk of wasting. However, despite a consensus for multimodal intervention (4), only 2 studies in this review implemented the recommended framework of combined pharmacological, nutritional, and exercise components (40, 49).

This review also helps highlight the controversy around terminology. This review sought to collate interventions for cachexia, a muscle-wasting condition with or without fat loss (5, 6). However, only 2 experimental studies provided a specific definition relating to cachexia (37, 49). Equally, a wide range of terminology, including malnutrition, PEW (43, 45–47), low FFMI, cachexia (40, 49), and cancer-related anorexia/cachexia syndrome (51), was used. Cancer cachexia has received the most research attention and currently has a consensus definition (1), unlike other chronic conditions. It is therefore not surprising that no multimodal intervention RCTs for other clinically relevant conditions (e.g., cardiac disease, RA) were reported. Currently, terminology indicating cachexia is being used interchangeably due to multiple generic operational definitions for wasting disorders. Experts have recommended terminology such as malnutrition for all wasting conditions as part of its continuum, with cachexia as an extreme form (53, 54).

Overall, there is a continued need for a more thorough understanding of the pathophysiology of cachexia and its progression, as this will lead to the development of combination therapies that are greatly needed. Although there is a consensus definition for cancer cachexia, no standardized treatment exists (3). Clinical studies are still needed to further explore the mechanisms of wasting in chronic illnesses and to discover novel therapies to prevent or reverse the development of cachexia (55). This will assist in the development of clinical practice guidelines to inform treatment pathways for patients with cachexia associated with a variety of advanced disease states.

The presence of cachexia is associated with high mortality and poor symptom status but also low QoL (12). Despite this, there continues to be gaps in the provision of QoL interventions and psychosocial support for patients experiencing wasting with advanced disease. No studies reported psychosocial interventions; however, several studies reported on QoL endpoints. It is important to acknowledge that a patient's relationship with food is negatively affected, which impacts social and family aspects. Future interventions should address the emotional and social context of such factors likely to impact eating problems, such as distress, anxiety, and support for family carers (7). Psychosocial support continues to be an unmet need in patients experiencing cachexia with advanced disease and should be included in the overall multimodal intervention framework (49).

Of note, all studies reported good acceptability, compliance, and safety profile of a wide range of intervention combinations. Solheim et al. (49) demonstrated that patients with advanced cancer who have a high risk of developing cachexia are willing and able to participate in an RCT of a complex intervention that includes a defined exercise program. The positive effect of this multimodal cachexia intervention on weight also highlights that cachexia need not be an inevitable consequence of advanced disease but may be attenuated through a multimodal intervention program (49). Limitations relate to a large number and wide range of outcomes, preventing meta-analysis. The durations of intervention varied between 6 wk to 24 mo, making comparison of effects difficult. Sample sizes were typically small and tended to lack power. For the sample sizes that were powered, caution should be applied to the interpretation of such small RCTs [e.g., (49)]. The diversity of patients (e.g., disease states) also makes it somewhat challenging to reach generic conclusions about cachexia in advanced disease. However, this review provides a unique collation and comparison of up-to-date RCTs for the treatment of severe wasting in advanced disease.

In conclusion, previous reviews have sought to summarize the applicability of multimodal interventions (17, 56), but this is the first critical review of multimodal interventions for cachexia. From research conducted to date, there is a clear consensus that single therapies will not stabilize or reverse cachexia (4). Taking into account the significant complexities of cachexia, a multimodal approach that includes a combination of pharmacology, exercise, and nutritional components is necessary. Accordingly, these studies report the role of multimodal interventions as positive and wide ranging, improving important clinical endpoints as well as QoL outcomes. This review also describes a good safety profile and compliance despite increased modes of intervention. Most important, this review highlights that well-conducted and powered RCTs are needed to test multimodal interventions to ascertain their true benefit for these populations. The number of patients who have cachexia and its consequential impact underscores the significance of this research direction. However, greater research collaboration, across chronic illnesses, will be required to tackle the complex challenge of severe wasting known as cachexia.

Acknowledgments

The authors' responsibilities were as follows—JR: is the principal investigator of this study; and all authors: assisted in the design of the study, revised the manuscript, and read and approved the final manuscript.

References

1. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12(5):489–95.
2. Morley JE, Thomas DR, Wilson MM. Cachexia: pathophysiology and clinical relevance. Am J Clin Nutr 2006;83(4):735–43.
3. Crawford J. What are the criteria for response to cachexia treatment? Ann Palliat Med 2019;8(1):43–9.
4. Di Girolamo FG, Guadagni M, Fiotti N, Situlin R, Biolo G. Contraction and nutrition interaction promotes anabolism in cachectic muscle. Curr Opin Clin Nutr Metab Care 2019;22(1):60–7.
5. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, Jatoi A, Kalantar-Zadeh K, Lochs H, Mantovani G, et al. Cachexia: a new definition. Clin Nutr 2008;27(6):793–9.
6. Mak RH, Ikizler AT, Kovesdy CP, Raj DS, Stenvinkel P, Kalantar-Zadeh K. Wasting in chronic kidney disease. J Cachexia Sarcopenia Muscle 2011;2(1):9–25.
7. Reid J, McKenna HP, Fitzsimons D, McCance TV. An exploration of the experience of cancer cachexia: what patients and their families want from healthcare professionals. Eur J Cancer Care (Engl) 2010;19(5):682–9.
8. Davis MP, Dickerson D. Cachexia and anorexia: cancer's covert killer. Support Care Cancer 2000;8(3):180–7.
9. Blum D, Strasser F. Cachexia assessment tools. Curr Opin Support Palliat Care 2011;5(4):350–5.
10. Strasser F. Diagnostic criteria of cachexia and their assessment: decreased muscle strength and fatigue. Curr Opin Clin Nutr Metab Care 2008;11(4):417–21.
11. Kazemi-Bajestani SM, Becher H, Fassbender K, Chu Q, Baracos VE. Concurrent evolution of cancer cachexia and heart failure: bilateral effects exist. J Cachexia Sarcopenia Muscle 2014;5(2):95–104.
12. von Haehling S, Anker MS, Anker SD. Prevalence and clinical impact of cachexia in chronic illness in Europe, USA, and Japan: facts and numbers update 2016. J Cachexia Sarcopenia Muscle 2016;7(5):507–9.
13. Saitoh M, Ishida J, Doehner W, von Haehling S, Anker MS, Coats AJS, Anker SD, Springer J. Sarcopenia, cachexia, and muscle performance in heart failure: review update 2016. Int J Cardiol 2017;238:5–11.
14. McDonald MN, Wouters EFM, Rutten E, Casaburi R, Rennard SI, Lomas DA, Bamman M, Celli B, Agusti A, Tal-Singer R, et al. It's more than low BMI: prevalence of cachexia and associated mortality in COPD. Respir Res 2019;20(1):100.

15. Santo RCE, Fernandes KZ, Lora PS, Filippin LI, Xavier RM. Prevalence of rheumatoid cachexia in rheumatoid arthritis: a systematic review and meta-analysis. J Cachexia Sarcopenia Muscle 2018;9(5): 816–25.
16. Ikizler TA, Cano NJ, Franch H, Fouque D, Himmelfarb J, Kalantar-Zadeh K, Kuhlmann MK, Stenvinkel P, TerWee P, Teta D, et al., Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. Kidney Int 2013;84:1096–107. 10.1038/ki.2013.147
17. Del Fabbro E. Combination therapy in cachexia. Ann Palliat Med 2019;8(1):59–66.
18. Fearon K, Argiles JM, Baracos VE, Bernabei R, Coats A, Crawford J, Deutz NE, Doehner W, Evans WJ, Ferrucci L, et al., Request for regulatory guidance for cancer cachexia intervention trials J Cachexia Sarcopenia Muscle 2015;6:272–4. 10.1002/jcsm.12083
19. Advani SM, Advani PG, VonVille HM, Jafri SH. Pharmacological management of cachexia in adult cancer patients: a systematic review of clinical trials. BMC Cancer 2018;18(1):1174.
20. Yeh SS, Marandi M, Thode HC, Levine DM, Parker T, Dixon T, Schuster MW., Report of a pilot, double-blind, placebo-controlled study of megestrol acetate in elderly dialysis patients with cachexia, J Ren Nutr 2010;20:52–62 10.1053/j.jrn.2009.08.005
21. Miki K, Maekura R, Nagaya N, Nakazato M, Kimura H, Murakami S, Ohnishi S, Hiraga T, Miki M, Kitada S, et al. Ghrelin treatment of cachectic patients with chronic obstructive pulmonary disease: a multicenter, randomized, double-blind, placebo-controlled trial. PLoS One 2012;7(5):e35708.
22. Rolfe M, Kamel A, Ahmed MM, Kramer J., Pharmacological management of cardiac cachexia: a review of potential therapy options, Heart Fail Rev 2019;24:617–23. 10.1007/s10741-019-09784-3
23. Grande AJ, Silva V, Maddocks M., Exercise for cancer cachexia in adults: executive summary of a Cochrane Collaboration systematic review, J Cachexia Sarcopenia Muscle 2015;6:208–11.10.1002/jcsm.12055
24. Lemmey AB, Marcora SM, Chester K, Wilson S, Casanova F, Maddison PJ. Effects of high-intensity resistance training in patients with rheumatoid arthritis: a randomized controlled trial. Arthritis Rheum 2009;61(12):1726–34.
25. Wilkinson TJ. Rheumatoid cachexia in rheumatoid arthritis patients treated in the current treat-to-target era: an exploration of the incidence, mechanisms, effects on physical function, and a potential nutritional treatment. Dissertation. Prifysgol Bangor University; 2016.
26. De Brandt J, Spruit MA, Derave W, Hansen D, Vanfleteren LE, Burtin C., Changes in structural and metabolic muscle characteristics following exercise-based interventions in patients with COPD: a systematic review. Expert Rev Respir Med 2016;10:521–45. 10.1586/17476348.2016.1157472
27. 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;91:210–21.10.1016/j.critrevonc.2014.02.005
28. Schols AM, Ferreira IM, Franssen FM, Gosker HR, Janssens W, Muscaritoli M, Pison C, Rutten-van Mölken M, Slinde F, Steiner MC, et al., Nutritional assessment and therapy in COPD: a European Respiratory Society statement. Eur Respir J 2014;44:1504–20 10.1183/09031936.00070914
29. Vest AR, Chan M, Deswal A, Givertz MM, Lekavich C, Lennie T, Litwin SE, Parsly L, Rodgers JE, Rich MW, et al., Nutrition, obesity, and cachexia in patients with heart failure: a consensus statement from the Heart Failure Society of America Scientific Statements Committee, J Card Fail 2019;25:380–400. S1071-9164(18)30917-5
30. Aversa Z, Costelli P, Muscaritoli M. Cancer-induced muscle wasting: latest findings in prevention and treatment. Ther Adv Med Oncol 2017;9(5):369–82.
31. Argilés JM, López-Soriano FJ, Stemmler B, Busquets S. Therapeutic strategies against cancer cachexia. Eur J Transl Myol 2019;29(1):7960.
32. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. Control Clin Trials 1996;17(1):1–12.
33. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
34. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. Published online April 26, 2020, doi: 10.1002/jrsm.1411. .
35. van Beers M, Rutten-van Mölken M, van de Bool C, Boland M, Kremers SPJ, Franssen FME, van Helvoort A, Gosker HR, Wouters EF, Schols A. Clinical outcome and cost-effectiveness of a 1-year nutritional intervention programme in COPD patients with low muscle mass: the randomized controlled NUTRAIN trial. Clin Nutr 2020;39(2):405–13.
36. Schutz Y, Kyle UU, Pichard C. Fat-free mass index and fat mass index percentiles in Caucasians aged 18–98 y. Int J Obes 2002;26(7):953–60.
37. Calder PC, Laviano A, Lonnqvist F, Muscaritoli M, Öhlander M, Schols A. Targeted medical nutrition for cachexia in chronic obstructive pulmonary disease: a randomized, controlled trial. J Cachexia Sarcopenia Muscle 2018;9(1):28–40.
38. van Wetering CR, Hoogendoorn M, Mol SJ, Rutten-van Mölken MP, Schols AM. Short- and long-term efficacy of a community-based COPD management programme in less advanced COPD: a randomised controlled trial. Thorax 2010;65(1):7–13.
39. Vermeeren MA, Creutzberg EC, Schols AM, Postma DS, Pieters WR, Roldaan AC, Wouters EF; COSMIC Study Group. Prevalence of nutritional depletion in a large out-patient population of patients with COPD. Respir Med 2006;100(8):1349–55.
40. Pison CM, Cano NJ, Chérion C, Caron F, Court-Fortune I, Antonini MT, Gonzalez-Bermejo J, Meziane L, Molano LC, Janssens JP, et al. Multimodal nutritional rehabilitation improves clinical outcomes of malnourished patients with chronic respiratory failure: a randomised controlled trial. Thorax 2011;66(11):953–60.
41. Kyle UG, Genton L, Karsegard L, Slosman DO, Pichard C. Single prediction equation for bioelectrical impedance analysis in adults aged 20–94 years. Nutrition 2001;17(3):248–53.
42. Baldi S, Aquilani R, Pinna GD, Poggi P, De Martini A, Bruschi C. Fat-free mass change after nutritional rehabilitation in weight losing COPD: role of insulin, C-reactive protein and tissue hypoxia. Int J Chron Obstruct Pulmon Dis 2010;5:29–39.
43. Hristea D, Deschamps T, Paris A, Lefrançois G, Collet V, Savoiu C, Ozenne S, Coupel S, Testa A, Magnard J. Combining intra-dialytic exercise and nutritional supplementation in malnourished older haemodialysis patients: towards better quality of life and autonomy. Nephrology (Carlton) 2016;21(9):785–90.
44. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kaysen G, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int 2008;73(4):391–8.
45. Jeong JH, Biruete A, Tomayko EJ, Wu PT, Fitschen P, Chung HR, Ali M, McAuley E, Fernhall B, Phillips SA, Wilund KR. Results from the randomized controlled IHOPE trial suggest no effects of oral protein supplementation and exercise training on physical function in hemodialysis patients. Kidney Int 2019;96(3): 777–86.
46. Dong J, Sundell MB, Pupim LB, Wu P, Shintani A, Ikizler TA. The effect of resistance exercise to augment long-term benefits of intradialytic oral nutritional supplementation in chronic hemodialysis patients. J Ren Nutr 2011;21(2):149–59.
47. Martin-Alemañy G, Valdez-Ortiz R, Olvera-Soto G, Gomez-Guerrero I, Aguire-Esquivel G, Cantu-Quintanilla G, Lopez-Alvarenga JC, Miranda-Alatriste P, Espinosa-Cuevas A. The effects of resistance exercise and oral nutritional supplementation during hemodialysis on indicators of nutritional status and quality of life. Nephrol Dial Transplant 2016;31(10):1712–20.

48. Uster A, Ruehlin M, Mey S, Gisi D, Knols R, Imoberdorf R, Pless M, Ballmer PE. Effects of nutrition and physical exercise intervention in palliative cancer patients: a randomized controlled trial. Clin Nutr 2018;37(4):1202–9.
49. Solheim TS, Laird BJA, Balstad TR, Stene GB, Bye A, Johns N, Pettersen CH, Fallon M, Fayers P, Fearon K, et al. A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer. J Cachexia Sarcopenia Muscle 2017;8(5):778–88.
50. Xu YJ, Cheng JC, Lee JM, Huang PM, Huang GH, Chen CC. A walk-and-eat intervention improves outcomes for patients with esophageal cancer undergoing neoadjuvant chemoradiotherapy. Oncologist 2015;20(10):1216–22.
51. Wen HS, Li X, Cao YZ, Zhang CC, Yang F, Shi YM, Peng LM. Clinical studies on the treatment of cancer cachexia with megestrol acetate plus thalidomide. Chemotherapy 2012;58(6):461–7.
52. Schink K, Reljic D, Herrmann HJ, Meyer J, Mackensen A, Neurath MF, Zopf Y. Whole-body electromyostimulation combined with individualized nutritional support improves body composition in patients with hematological malignancies—a pilot study. Front Physiol 2018;9:1808.
53. Koppe L, Fouque D, Kalantar-Zadeh K. Kidney cachexia or protein-energy wasting in chronic kidney disease: facts and numbers. J Cachexia Sarcopenia Muscle 2019;10(3):479–84.
54. Sánchez-Rodríguez D, Annweiler C, Cederholm T. A translational approach for the clinical application of recently updated definitions of malnutrition (GLIM) and sarcopenia (EWGSOP2). Maturitas 2019;122:89–90.
55. Scherbakov N, Doehner W., Cachexia as a common characteristic in multiple chronic disease. J Cachexia Sarcopenia Muscle (2018) ;9:1189–91. doi: 10.1002/jcsm.12388
56. Aapro M, Arends J, Bozzetti F, Fearon K, Grunberg SM, Herrstedt J, Hopkinson J, Jacquelin-Ravel N, Jatoi A, Kaasa S, et al. Early recognition of malnutrition and cachexia in the cancer patient: a position paper of a European School of Oncology Task Force. Ann Oncol 2014;25(8):1492–9.