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Randomized Control Trials

Clinical outcome and cost-effectiveness of a 1-year nutritional intervention programme in COPD patients with low muscle mass: The randomized controlled NUTRAIN trial

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SUMMARY

Background and aims: The efficacy of nutritional intervention to enhance short- and long-term outcomes of pulmonary rehabilitation in COPD is still unclear, hence this paper aims to investigate the clinical outcome and cost-effectiveness of a 12-month nutritional intervention strategy in muscle-wasted COPD patients.

Methods: Prior to a 4-month pulmonary rehabilitation programme, 81 muscle-wasted COPD patients (51% males, aged 62.5 ± 0.9 years) with moderate airflow obstruction (FEV_1 55.1 ± 2.2% predicted) and impaired exercise capacity (W_{max} 63.5 ± 2.4% predicted) were randomized to 3 portions of nutritional supplementation per day (enriched with leucine, vitamin D and polyunsaturated fatty acids) [NUTRITION] or PLACEBO (phase 1). In the unblinded 8-month maintenance phase (phase 2), both groups received structured feedback on their physical activity level assessed by accelerometry. NUTRITION additionally received 1 portion of supplemental nutrition per day and motivational interviewing-based nutritional counselling. A 3-month follow-up (phase 3) was included.

Results: After 12 months, physical capacity measured by quadriceps muscle strength and cycle endurance time were not different, but physical activity was higher in NUTRITION than in PLACEBO (Δ1030 steps/day, $p = 0.025$). Plasma levels of the enriched nutrients ($p < 0.001$) were higher in NUTRITION than PLACEBO. Trends towards weight gain in NUTRITION and weight loss in PLACEBO led to a significant between-group difference after 12 months (Δ1.54 kg, $p = 0.041$). The HADS anxiety and depression scores improved in NUTRITION only (Δ-1.92 points, $p = 0.037$). Generic quality of life (EQ-5D) was decreased in PLACEBO but not in NUTRITION (between-group difference after 15 months 0.072 points, $p = 0.009$). Overall motivation towards exercising and healthy eating was high and did not change significantly after 12 months; only amotivation towards healthy eating yielded a significant between-group difference (Δ1.022 points, $p = 0.015$). The cost per quality-adjusted life-year after 15 months was EUR 16,750.

Conclusions: Nutritional intervention in muscle-wasted patients with moderate COPD does not enhance long-term outcome of exercise training on physical capacity but ameliorates plasma levels of the

Abbreviations: BMI, Body mass index; BREQ-2, Behavioural Regulation in Exercise Questionnaire-2; CET, Cycle endurance time; COPD, Chronic obstructive pulmonary disease; DEXA, Dual energy x-ray absorptiometry; DHA, Docosahexaenoic acid; DLCO, Diffusion capacity of the lung for carbon monoxide; EPA, Eicasopentaenoic acid; EQ-5D-3L, EuroQol Five-Dimensions Questionnaire; FEV_1, Forced expiratory volume in 1 s; FVC, Forced vital capacity; FFMI, Fat-free mass index; HADS, Hospital Anxiety and Depression Scale; ICER, Incremental cost-effectiveness ratio; MI, Motivational interviewing; PA, Physical activity; PAL, physical activity level; PR, Pulmonary rehabilitation; PUFA, Polyunsaturated fatty acids; QALY, Quality-adjusted life year; QMS, Quadriceps muscle strength; REBS, Regulation of Eating Behaviour Scale; SDT, Self-determination theory; SGRQ, St George's Respiratory Questionnaire.

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supplemented nutrients, total body weight, physical activity and generic health status, at an acceptable increase of costs for patients with high disease burden.

1. Introduction

Extra-pulmonary pathology enhances disease burden in patients with chronic obstructive pulmonary disease (COPD) [1]. Decreased muscle mass is associated with increased prevalence of osteoporosis, lower muscle strength and exercise performance, and increased mortality risk [2]. Furthermore, COPD is characterized by impaired muscle oxidative metabolism, which cannot simply be explained by disuse alone [3,4] and may predominate in patients with low muscle mass [5].

Exercise training is a cornerstone of pulmonary rehabilitation (PR) [6], and improves lower limb muscle strength, exercise performance, and in some studies also daily physical activity level [7,8]. Protein and specific nutrient supplementation could potentiate the effects of PR or represent an alternative to exercise training in severely deconditioned patients. In contrast to other nutrients including creatine and nitrate [9], to date only polyunsaturated fatty acids (PUFA) [10] and vitamin D [11] have been effective as single-nutrient add-on treatment in COPD by enhancing inspiratory muscle strength [11] and maximal oxygen uptake [10,11] during PR which could be via immune modulation and/or boosting oxidative metabolism. Multimodal nutritional interventions are interesting to explore because the regulation of muscle mass and metabolism is controlled by multiple tightly intertwined pathways [12]. In the NUTRAIN trial [13], we developed a multimodal stepwise nutritional intervention approach including high-quality protein enriched with leucine, vitamin D, and omega-3 PUFA, based on evidence regarding the mode of action of these nutrients on skeletal muscle maintenance, combined with reported deficiencies in COPD. The nutritional supplementation was supported by nutritional counselling. This approach was investigated in COPD patients with low muscle mass as a susceptible group for accelerated functional decline [14]. The results of the first phase, which took place during PR, have been reported earlier [13]. During this phase nutritional supplementation improved nutritional status but did not enhance lower limb muscle strength or muscle mass regain. A remarkable between-group difference was shown in physical activity level, largely due to a decline in the PLACEBO group only, whereas the NUTRITION group remained stable, indicating that this nutritional strategy might be effective to attenuate the decline in physical activity typically observed in patients with COPD [15]. Exercise-induced muscle fatigue is a commonly reported symptom in COPD [16], and nutritional modulation thereof or nutritional effects beyond the muscle (i.e., the brain or cardiovascular system) [17,18] might explain this observation. Accordingly, Calder et al. [19] showed in a 3-month randomized controlled trial that supplementation with high-quality protein enriched with omega-3 PUFA and vitamin D, reduced walking exercise-induced fatigue (measured using the Borg scale) in COPD patients with low muscle mass.

We hypothesized that improved nutritional status and positive effects on daily physical activity level might also enhance the long-term efficacy of the intervention with quadriceps muscle strength (QMS) as primary outcome. The current paper aims to investigate the clinical outcome of the overall nutritional management strategy of the NUTRAIN trial, including phase 1, the 8-month maintenance phase after completion of PR (phase 2) and the 3-month follow-up (phase 3). Furthermore, the cost-effectiveness of the intervention after 15 months is explored.

2. Methods

2.1. Study design

The trial was integrated in the outpatient PR programme of 7 hospitals in the Netherlands (Sint Anna hospital in Geldrop, Maxima Medical Centre in Veldhoven (until March 2013), Laurentius hospital in Roermond, Sint Jans Gasthuis hospital in Weert, Elkerliek hospital in Helmond, Maastricht University Medical Centre and Catharina hospital in Eindhoven), supervised by CIRO, a centre of expertise for patients with chronic organ failure in Horn. Participants were recruited during the assessment period at CIRO when eligible for outpatient PR at one of the hospitals. Patients with severe COPD referred for inpatient PR at CIRO were not included. Every participant underwent an interview with a chest physician at admission; the study physician checked eligibility of potential participants during this visit and asked participants whether they could be contacted by the researcher. The study was registered at clinicaltrials.gov (NCT01344135) and the Medical Ethics Committee of Maastricht University Medical Centre granted ethical approval (NL34927068.10/MEC 11-3-004). All participants provided written informed consent.

The intervention was divided into a 4-month nutritional intervention (phase 1) and an 8-month maintenance phase (phase 2). In short, in the double-blind controlled intervention phase 1, 81 patients were randomized to the PLACEBO ($n = 39$) or NUTRITION group ($n = 42$). Both groups underwent a supervised centre-based exercise training programme and were advised to consume 3 oral nutritional supplements daily. The NUTRITION product provided protein, carbohydrates, fat and micronutrients, and was enriched with leucine, omega-3 PUFA, and vitamin D (Nutricia NV, Zoetermeer, The Netherlands). The PLACEBO product did not comprise the active components, but consisted of a flavoured non-caloric cloudified aqueous solution. For details see Van de Bool et al. [13].

In the open-label maintenance phase (phase 2), both groups received feedback on their physical activity behaviour twice, based on accelerometry. This was done in order to offer both groups a follow-up intervention aimed at maintaining long-term efficacy of the exercise training. In addition, participants in NUTRITION were advised to take 1 oral nutritional supplement per day and received four nutritional counselling sessions. These were provided by trained nurses, and aimed to optimize participants' dietary habits and maximize adherence to a healthy diet and the supplement regime. The counselling was based on self-determination theory (SDT) [20], which assumes that autonomous forms of motivation are essential to achieve lasting behavioural change, and it was operationalized through motivational interviewing (MI) [21]. After the 8-month maintenance phase, participants were followed up for three months, without any intervention taking place in either group (phase 3). Figure 1 depicts a flowchart of the study; Fig. 2 outlines the study design.

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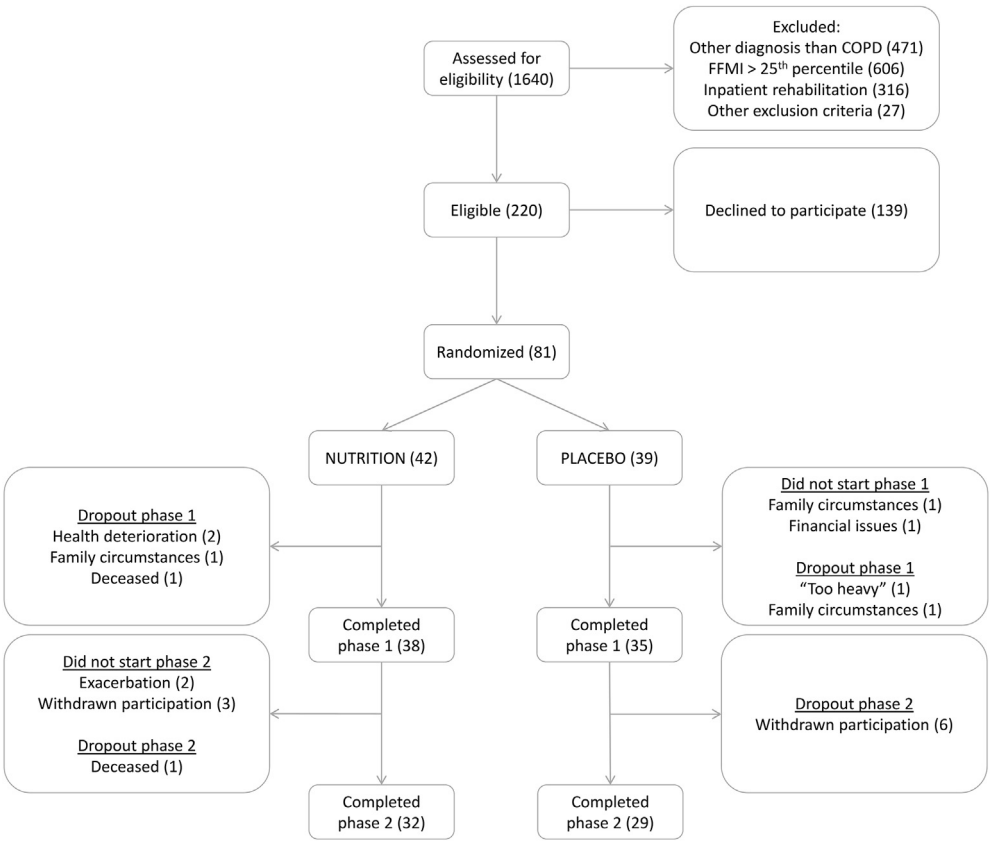

Fig. 1. Consort flow chart.

2.2. Patients

Patients with COPD (post-bronchodilator FEV_1 / FVC < 0.7) referred for outpatient PR between September 2011 and April 2014 were eligible for participation if they had low muscle mass, defined as a fat-free mass index (FFMI) below the sex- and age-specific 25th percentile FFMI-values [22]. Exclusion criteria were age under 18 years old, allergy or intolerance to components of the study product, investigator's uncertainty about patient's willingness or ability to comply with the protocol requirements, inability to stop current supplement use, participation in any other study involving investigational or marketed products concomitantly or less than two weeks prior to entry into the study, pregnancy, or life-threatening diseases.

2.3. Outcomes

Quadriceps muscle strength (QMS), assessed by dynamometry (System 4 Pro; Biodex Medical Systems Inc., New York, USA), served as the primary outcome of this study. QMS, body composition measured by dual energy x-ray absorptiometry (DEXA) (Lunar Prodigy system; GE Healthcare, Madison, WI, USA), cycle endurance time (CET) on a cycle ergometer (Carefusion, Houten, The Netherlands) (determined during the constant work rate cycling endurance test at 75% of the peak workload), and fasting plasma levels of vitamin D, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and leucine were measured at baseline (before entering PR), and after phase 1 and 2. Habitual dietary intake of the last month was assessed at these time points by trained dieticians using a validated cross-check dietary history method and calculated using the Dutch Food Composition Database. Mental and physical health status, assessed by the Hospital Anxiety and Depression Scale (HADS) [23], EuroQoL Five-Dimensions Questionnaire (EQ-5D-3L) [24], St George's Respiratory Questionnaire (SGRQ) [25], and PAL (physical activity level) as assessed by daily steps by a tri-axial GT3X Actigraph accelerometer (Health One Technology, Fort Walton Beach, FL, USA) were measured at baseline and after phase 1, 2 and 3. Post-bronchodilator forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were assessed by standardised equipment (Masterlab®; Jaeger, Wurzburg, Germany), in accordance with the latest GOLD guidelines [26]. The Dutch value set was used to transform EQ-5D scores into utilities [27]. Adopting such a wide range of outcome measures is in line with the recommendations of the joint ATS/ERS task force on outcome measures in COPD to use a multi-outcome approach [28].

Participants' motivational profiles towards exercising and healthy eating were assessed using the Behavioural Regulation in Exercise Questionnaire-2 (BREQ-2) [29] and the Regulation of Eating Behaviour Scale (REBS) [30], respectively, at baseline and after phase 1, 2 and 3. These questionnaires are based on SDT and they provide six subscale scores (see [20] for details). Answers were given on a 5-point Likert scale in both questionnaires. Scores on the BREQ subscales range from 1 (lowest possible motivation) to 5 (highest possible motivation). Scores on the REBS range from 0 (lowest possible motivation) to 10 (highest possible motivation). Internal consistency measured by Cronbach's α was adequate for all scales, except for identified regulation towards exercising ($\alpha = 0.319$ after phase 2). Consequently, this scale was excluded from subsequent analyses.

2.4. Costs

Total costs (not only related to COPD) were calculated from a healthcare and a societal perspective. The healthcare perspective

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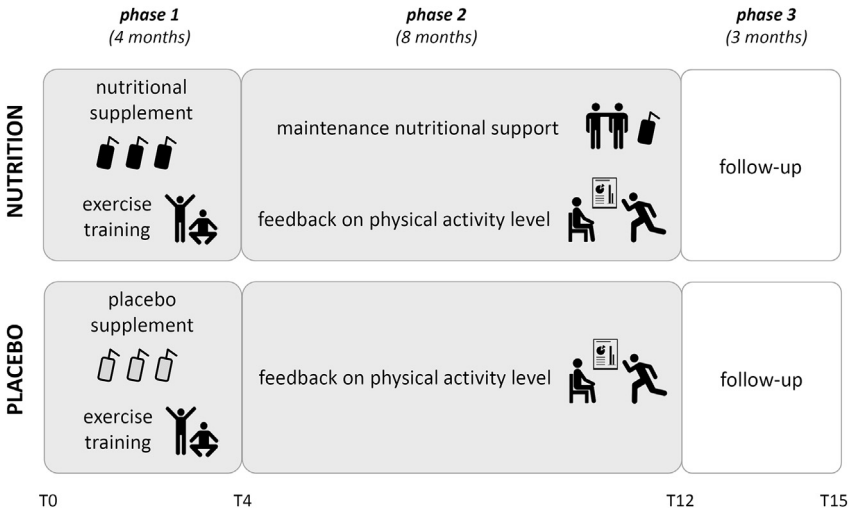

Fig. 2. Study design of the NUTRAIN trial.

included all costs covered by the healthcare budget. The societal perspective additionally included travel costs and costs of productivity loss due to absence from paid work (absenteeism). Healthcare utilization, travel distance, and absenteeism were assessed in a resource use questionnaire after phase 1, 2 and 3.

The intervention costs included the reported number of supervised exercise training sessions and their duration, the number of nutritional supplements used, the number of educational counselling sessions and their duration, the number of consultations for physical activity level feedback, the number of nutritional counselling sessions, and the travel distance to health care providers.

Standard unit costs were determined using Dutch guideline prices [31] and inflated to 2015 values using the general consumer price index [32]. The costs of medication were obtained from the Drug Information System of the Dutch National Health Care Institute and included value added tax and pharmacist dispensing fees [33]. The productivity costs were estimated using the Friction Cost Approach, which assumes that productivity loss occurs as long as a sick employee is not replaced (the friction period) [34]. We used a friction period of 85 days. The unit costs are shown in Supplementary Tables 1 and 2.

2.5. Statistical analyses

Statistical analyses were performed using Stata, in accordance with the intention-to-treat principle.

Plasma levels of the supplemented nutrients, body composition, motivational profile and physical function were analysed using a linear repeated measurement model with correlated error terms and unstructured covariance matrix. The model included treatment, time (i.e., the measurements at 4 and 12 months) and treatment by time interactions. Data from patients who discontinued the trial prematurely were included in the analyses up to the point of drop-out.

Costs were also analysed in a linear repeated measures model with correlated error terms and unstructured covariance matrix. The dependent variable was total costs in a certain phase, and the explanatory variables were time (4, 12, and 15 months) and the interaction of treatment and time. The results were used to predict the mean costs per treatment group for each phase. Total costs were calculated as the sum of the predicted costs of the rehabilitation phase, maintenance phase, and follow-up phase.

To assess differences in health outcomes between the two treatment groups, we also used linear repeated measurement models with correlated errors and unstructured covariance matrix. Explanatory variables were time (4, 12 [and, if applicable, 15] months) and the interaction of treatment and time. We calculated the number of quality-adjusted life-years (QALYs) for each patient as the area under the predicted utility curve, using linear interpolation between two measurements.

The costs per gained QALY were calculated as the difference in total costs between the two groups divided by the difference in QALYs. Uncertainty around this cost-effectiveness ratio was estimated by performing 5000 bootstrap replications.

2.6. Power calculation

The power calculation was based on the INTERCOM study assuming a 10% between-group difference in peak torque assuming maintenance of skeletal muscle strength in NUTRITION during follow-up and a standard deviation of 5 Nm in peak torque. Allowing for 25% drop-out yielded a subgroup size of $n = 60$. Patient inclusion was prematurely discontinued because the test product could not be produced within the appropriate quality specifications due to discontinuation of the supply of one of the ingredients, but the sample size was justifiable based on other RCTs published in the meantime [13].

3. Results

3.1. Patients

Baseline characteristics did not differ between the groups, except for a higher peak workload in NUTRITION. The study population consisted of 51% males, aged 62.5 ± 0.9 years, and was characterized by low diffusion capacity (DLCO 49.4 ± 1.7%), moderate airflow limitation (FEV_1 55.1 ± 2.2% predicted), normal to low BMI (22.7 ± 0.3 kg/m^2), impaired exercise capacity (W_{max} 63.5 ± 2.4% predicted), and low FFMI (15.8 ± 1.6 kg/m^2) (see Table 1).

3.2. Physical functioning

No between-group difference was observed in improved physical capacity (QMS and CET) (see Table 2). When QMS was

Table 1
Baseline characteristics.

	NUTRITION	PLACEBO
	Mean ± SE	Mean ± SE
General		
Gender (% male)	42.9%	59.0%
Age (years)	62.8 ± 1.3	62.2 ± 1.3
Current smokers (%)	19.0%	31.6%
Low SES (no or only primary education) (%)	5.6%	13.3%
Employed (%)	33.3%	19.4%
Number of exacerbations in the last year	1.1 ± 0.2	1.4 ± 0.3
Lung function		
FEV_1 (% predicted)	57.0 ± 3.3	53.0 ± 2.8
FVC (% predicted)	102.8 ± 2.9	100.6 ± 2.7
FEV_1/FVC (%)	44.4 ± 2.0	41.6 ± 1.8
FRC (% predicted)	139.1 ± 4.3	146.7 ± 5.9
Residual volume (% predicted)	143.4 ± 6.3	153.1 ± 8.5
DLCO (% predicted)	51.4 ± 2.2	47.1 ± 2.5
Physical function		
QMS (Nm)	121.5 ± 6.4	118.0 ± 6.6
CET (s)	319.0 ± 35.2	231.5 ± 12.0
Peak workload (Wmax)	84.6 ± 5.2	72.5 ± 3.8
Peak workload (% predicted)	69.5 ± 3.3**	57.0 ± 3.4
PAL (steps/day)	4716.7 ± 327.2	4516.6 ± 379.3
Dietary intake		
Energy (kcal)	2426.0 ± 168.0	2442.8 ± 174.2
Protein (g)	91.1 ± 5.5	89.9 ± 5.5
Carbohydrates (g)	263.1 ± 19.9	266.8 ± 17.5
Fat (g)	103.1 ± 9.8	105.4 ± 12.3
PUFA (g)	20.2 ± 2.0	21.5 ± 2.7
Cholesterol (mg)	251.5 ± 25.2	239.1 ± 25.2
Dietary fiber (g)	21.9 ± 1.3	21.7 ± 1.6
Calcium (mg)	1083.5 ± 96.1	977.3 ± 67.5
Vitamin A (μg)	1241.4 ± 96.5	1192.5 ± 145.8
Vitamin C (mg)	84.1 ± 6.1	85.9 ± 6.9
Vitamin D (μg)	5.3 ± 0.4	5.1 ± 0.6
Vitamin E (mg)	14.6 ± 1.3	13.9 ± 1.2
Supplemented plasma nutrient levels		
Leucine (μmol/l)	147.7 ± 3.6	153.5 ± 3.5
Vitamin D (nmol/l)	54.0 ± 4.5	45.3 ± 3.1
EPA (mg/l)	1.1 ± 0.1	1.2 ± 0.1
DHA (mg/l)	2.9 ± 0.2	3.2 ± 0.2
Body composition		
Total weight (kg)	64.3 ± 1.6	65.0 ± 1.7
BMC (g)	2331.3 ± 73.0	2414.7 ± 82.3
ASM (kg)	17.4 ± 0.6	18.4 ± 0.6
Fat mass (kg)	20.0 ± 1.0	19.0 ± 1.3
Lean mass (kg)	42.0 ± 1.3	43.6 ± 1.2
BMI (kg/m^2)	22.9 ± 0.4	22.6 ± 0.5
FFMI (kg/m^2)	15.7 ± 0.3	15.9 ± 0.2
Patient-reported outcomes		
EQ-5D	0.8 ± 0.0	0.8 ± 0.0
SGRQ	49.9 ± 2.4	50.1 ± 2.6
HADS Total	10.9 ± 1.2	10.2 ± 1.1

SES: socio-economic status; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; FRC: functional residual capacity; DLCO: diffusion capacity of the lung for carbon monoxide; QMS: quadriceps muscle strength; CET: cycle endurance time; PAL: physical activity level; PUFA: polyunsaturated fatty acids; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; BMC: bone mineral content; ASM: appendicular skeletal muscle mass; BMI: body mass index; FFMI: fat-free mass index; EQ-5D: EuroQoL 5-dimensions questionnaire; SGRQ: St George's Respiratory Questionnaire; HADS: Hospital Anxiety and Depression Scale. $^{**}p < 0.01$.

normalized for appendicular lean mass or fat-free mass, the between-group difference was not significant either (data not shown). Physical activity level was significantly lower compared to baseline in PLACEBO whereas it remained stable in NUTRITION. This led to a significant between-group difference on number of steps per day ($p = 0.025$) (see Fig. 3). Activity intensity did not differ significantly over time or between the groups: in both groups across all time points, patients spent around 70% in sedentary physical activity (PA), 23% in lifestyle PA, 6% in light PA and 1% in moderate-to-vigorous PA.

The change in physical activity level from baseline to T12 correlated significantly with the change in appendicular skeletal muscle mass index (ASMI) ($r = 0.371$, $p = 0.022$) but not that in total body weight ($r = 0.088$, n.s.) in the entire study population.

3.3. Dietary intake and plasma nutrient status

Overall dietary habits represented a typical Western diet and no significant within- or between-group changes were identified throughout the trial on any macronutrient or micronutrient, except for cholesterol intake (see Supplementary Table 1). Cholesterol intake was significantly higher in PLACEBO after 12 months compared to baseline ($p = 0.001$), leading to a significant between-group difference ($p = 0.003$). At baseline, 31.2% of participants had vitamin D insufficiency, whereas 57.5% had vitamin D deficiency.

Plasma vitamin D, EPA and DHA levels were significantly increased compared to baseline in NUTRITION. EPA levels were significantly decreased compared to baseline in PLACEBO. Leucine, vitamin D, EPA and DHA levels significantly differed between groups (see Table 2).

3.4. Body composition

Total body weight, muscle mass and fat mass tended to decrease within PLACEBO and tended to increase within NUTRITION from baseline to the end of phase 2. This resulted in a significant between-group difference in total body weight change, in favour of NUTRITION (Δ1.54 ± 0.76 kg, $p = 0.041$) (see Table 2 and Fig. 4).

3.5. Patient-reported outcomes

Total HADS score significantly improved in NUTRITION ($p = 0.037$). In PLACEBO, the EQ-5D score decreased significantly ($p = 0.009$) (see Table 2). The SGRQ did not differ significantly within or between groups. After phase 3, EQ-5D utility was still significantly decreased compared to baseline in PLACEBO ($p = 0.011$), whereas the between-group difference was also significant in favour of NUTRITION, $p = 0.034$) (see Table 3).

Interestingly, the change in EQ-5D scores from baseline to T12 correlated significantly with the change in total body weight ($r = 0.406$, $p = 0.008$) and ASMI ($r = 0.456$, $p = 0.003$) in the entire study population.

3.6. Motivational profile

Motivation towards both exercising and healthy eating was already high before the counselling sessions started. The mean scores for intrinsic and identified motivation towards exercising before the counselling started were 4.14 and 4.03 out of 5, respectively. These figures were 7.69 and 8.42 out of 10 for intrinsic and identified motivation towards healthy eating. In NUTRITION, amotivation towards exercising decreased ($p = 0.015$), while in PLACEBO, identified motivation towards healthy eating decreased ($p = 0.019$). Only amotivation towards healthy eating differed significantly between groups ($p = 0.015$) (see Table 4).

3.7. Intervention costs

Intervention costs are presented in Supplementary Table 1. From a healthcare perspective, the mean intervention costs of the total intervention were EUR 2233 per patient in NUTRITION and EUR 1372 in PLACEBO. From a societal perspective, these costs were EUR 2265 and EUR 1404, respectively. The between-group difference is mainly due to the costs of nutritional supplements. Supervised

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Table 2
Within- and between-group differences in plasma nutrient status, physical function, body composition, and patient-reported outcomes, after 12 months.

Measure	Within-group				Between-group	
	NUTRITION		PLACEBO			
	adj. *M* (*SE*)	*Z*	adj. *M* (*SE*)	*Z*	adj. *M* (*SE*)	*Z*
Physical function						
QMS (Nm)	10.35 (3.51)	2.95**	10.05 (3.46)	2.90**	0.30 (4.92)	0.06
CET (s)	107.1 (62.9)	1.70*	200.3 (64.5)	3.11**	−93.2 (89.8)	1.04
PAL (steps/day)	358.8 (339.9)	1.06	−671.3 (330.3)	−2.03*	1030.1 (459.8)	2.24*
Supplemented plasma nutrient levels						
Leucine (μmol/l)	10.41 (5.57)	1.87	−6.08 (5.80)	−1.05	16.49 (8.01)	2.06*
Vitamin D (nmol/l)	15.10 (2.69)	5.61***	1.25 (2.77)	0.45	13.85 (3.84)	3.60***
EPA (mg/l)	5.42 (1.66)	3.27**	−3.34 (1.64)	−2.04*	8.76 (1.95)	4.49***
DHA (mg/l)	7.26 (2.69)	2.70**	−4.69 (2.67)	−1.76	11.97 (3.47)	3.45**
Body composition						
Total weight (kg)	0.64 (0.53)	1.21	−0.90 (0.54)	−1.67	1.54 (0.76)	2.04*
BMC (g)	−9.96 (13.81)	−0.72	−22.21 (14.12)	−1.57	12.26 (19.73)	0.62
ASM (kg)	0.17 (0.21)	0.83	−0.22 (0.21)	−1.02	0.39 (0.29)	1.32
Fat mass (kg)	0.86 (0.50)	1.71	−0.47 (0.51)	−0.91	1.33 (0.72)	1.86
Patient-reported outcomes						
EQ-5D	−0.003 (0.03)	−0.10	−0.07 (0.03)	−2.63**	0.07 (0.04)	1.86
SGRQ	1.43 (1.89)	0.75	−0.71 (1.97)	−0.04	2.14 (2.73)	0.78
HADS Total	−1.92 (0.92)	−2.09*	−1.50 (0.97)	−1.54	−0.42 (1.30)	−0.32

Values shown as changes from baseline. QMS: quadriceps muscle strength; Nm: Newtonmeter; CET: cycle endurance time; PAL: physical activity level; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; BMC: bone mineral content; ASM: appendicular skeletal muscle mass; EQ-5D: EuroQoL 5-dimensions questionnaire; SGRQ: St George's Respiratory Questionnaire; HADS: Hospital Anxiety and Depression Scale. *$p < 0.05$ **$p < 0.01$ ***$p < 0.001$.

exercise training was the main driver of the intervention costs in both groups.

3.8. Total costs and cost-effectiveness

Table 5 shows the cost-effectiveness analysis after phase 2 and 3. The differences in various categories of healthcare utilization and costs over 12 and 15 months are presented in Supplementary Tables 2 and 3. After phase 2, the costs in NUTRITION were estimated to be EUR 1529 (certainty 87%) higher than in PLACEBO from the healthcare perspective and EUR 2829 (certainty 98%) higher from the societal perspective. After phase 3, costs in NUTRITION were EUR 670 (certainty 64%) higher from the healthcare perspective and EUR 2401 (certainty 92%) higher from the societal perspective.

Both from a healthcare and societal perspective, the point-estimates of costs pointed towards higher costs in NUTRITION and a higher physical activity level in NUTRITION after phase 2, and a higher number of QALYs in NUTRITION after phase 3. The probability that the nutritional intervention was cost-effective at a willingness-to-pay of EUR 20,000 and EUR 80,000 per QALY was 27% and 59% (after phase 2), and 55% and 82% (after phase 3) (data not shown).

4. Discussion

This paper investigated the clinical benefits and cost-efficacy of a 12-month multimodal, stepwise nutritional intervention

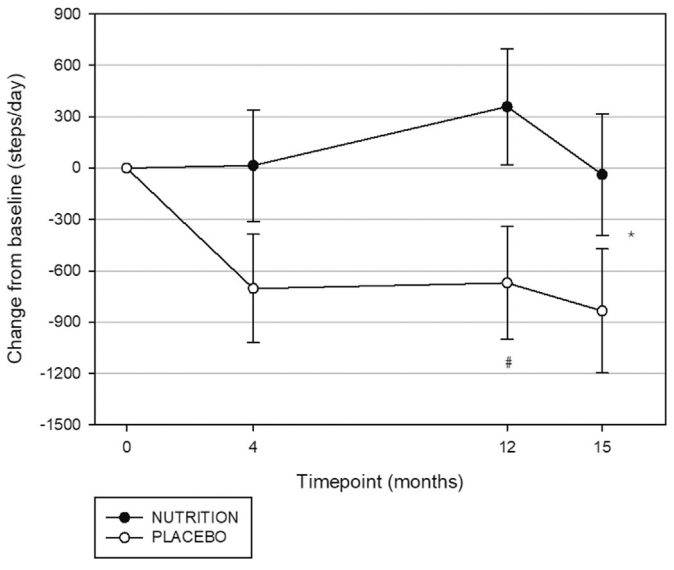

Fig. 3. Development of physical activity level as change from baseline. # within-group $p < 0.05$ (compared to baseline); *between-group $p < 0.05$.

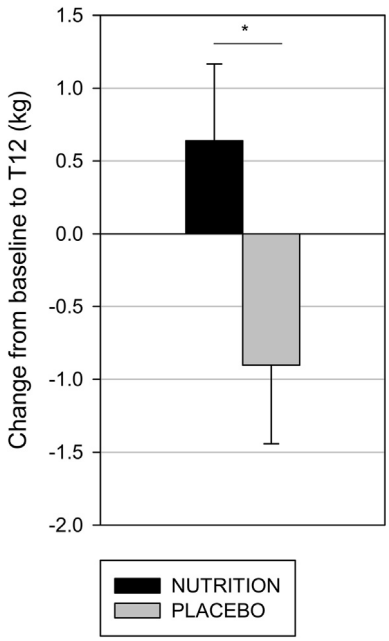

Fig. 4. Change in total body weight from baseline to T12. *between-group $p < 0.05$.

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Table 3
Within- and between-group differences in physical activity level and patient-reported outcomes, after 15 months.

Measure	Within-group				Between-group	
	NUTRITION		PLACEBO			
	adj. *M* (*SE*)	*Z*	adj. *M* (*SE*)	*Z*	adj. *M* (*SE*)	*Z*
PAL (steps/day)	−38.1 (355.5)	−0.11	−834.2 (362.8)	−2.30*	796.1 (496.9)	1.60
EQ-5D	0.012 (0.02)	0.49	−0.060 (0.02)	−2.53*	0.072 (0.03)	2.12*
SGRQ	0.16 (2.11)	0.08	2.72 (2.19)	1.24	−2.56 (3.00)	−0.86
HADS Total	−0.85 (0.97)	−0.87	−1.74 (0.98)	−1.78	0.89 (1.38)	0.65

Values shown as changes from baseline. PAL: physical activity level; EQ-5D: EuroQoL 5-dimensions questionnaire; SGRQ: St George's Respiratory Questionnaire; HADS: Hospital Anxiety and Depression Scale. *$p < 0.05$.

Table 4
Within- and between-group differences in motivational profile, after 12 months.

Measure	Within-group				Between-group	
	NUTRITION		PLACEBO			
	adj. *M* (*SE*)	*Z*	adj. *M* (*SE*)	*Z*	adj. *M* (*SE*)	*Z*
Exercise						
Intrinsic	0.069 (0.11)	0.60	0.011 (0.12)	0.09	0.058 (0.16)	0.36
Introjected	−0.183 (0.16)	−1.12	0.212 (0.17)	1.25	−0.396 (0.23)	−1.72
External	0.006 (0.10)	0.06	−0.006 (0.10)	−0.06	0.012 (0.13)	0.09
Amotivation	−0.232 (0.10)	−2.43*	−0.011 (0.10)	−0.17	−0.215 (0.13)	−1.71
Healthy eating						
Intrinsic	−0.094 (0.26)	−0.36	0.060 (0.27)	0.22	−0.154 (0.37)	−0.42
Integrated	0.040 (0.29)	0.14	−0.230 (0.31)	−0.76	0.271 (0.40)	0.67
Identified	−0.028 (0.24)	−0.12	−0.577 (0.24)	−2.35*	0.549 (0.34)	1.60
Introjected	−0.437 (0.29)	−1.50	−0.644 (0.30)	−0.21	−0.373 (0.41)	−0.91
External	−0.297 (0.38)	−0.78	−0.122 (0.39)	−0.31	−0.175 (0.53)	−0.33
Amotivation	−0.429 (0.30)	−1.44	0.593 (0.31)	1.92	−1.022 (0.42)	−2.43*

Values shown as change from baseline. *$p < 0.05$.

strategy in patients with moderate COPD and low muscle mass. Physical capacity, as primary outcome, was improved in both groups after 12 months, but NUTRITION took 1030 additional steps per day compared to PLACEBO. This difference exceeds the minimal important difference to reduce risk of hospital admission [35], and it cannot be explained by greater energy substrate availability, as total macronutrient intake was not significantly different between the groups at T12 (data not shown). This indicates that nutrient-specific mechanisms could explain the dissociation between changes in QMS and physical activity via various synergistic pathways including immune modulation (PUFA, vitamin D) [36,37], enhancing muscle oxidative metabolism (PUFA) [38] and modifying muscle maintenance regulation (PUFA, leucine) [39,40].

Table 5
Cost-effectiveness and cost-utility: 12 and 15 month time horizon.

12 month time horizon	NUTRITION	PLACEBO	Difference (95% UI)
Costs (euros)			
Healthcare perspective (HCP)	8094	6565	1529 (−1007 to 4343)
Societal perspective (SP)	9404	6575	2829 (100 to 5802)
Effects			
QALYs	0.66	0.64	0.025 (−0.02 to 0.07)
PAL (steps/day)	4960	3940	1020 (17 to 1990)
Percentage of patients with +4 units improvement in SGRQ	0.36	0.43	−0.07 (−0.38 to 0.22)
ICER (euros)	*HCP*	*SP*	
Costs/QALY gained	61,160	113,160	
Costs/1000 additional steps	1499	2774	
Cost/additional patient with +4 units improvement in SGRQ	dominated	dominated	
15 month time horizon	**NUTRITION**	**PLACEBO**	**Difference (95% UI)**
Costs (euros)			
Healthcare perspective (HCP)	9548	8878	670 (−2468 to 4001)
Societal perspective (SP)	11,324	8923	2401 (−854 to 5824)
Effects			
QALYs	0.86	0.82	0.04 (−0.01 to 0.10)
PAL (steps/day)	4576	3780	814 (−335 to 1838)
Percentage of patients with +4 units improvement in SGRQ	0.35	0.23	0.12 (−0.16 to 0.39)
ICER (euros)	HCP	SP	
Costs/QALY gained	16,750	60,025	
Costs/1000 additional steps	823	2950	
Cost/additional patient with +4 units improvement in SGRQ	5583	20,008	

*$p < 0.05$. UI: uncertainty interval; HCP: healthcare perspective; SP: societal perspective; QALY: quality-adjusted life year; SGRQ: St George's Respiratory Questionnaire.

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Plasma levels of the supplemented nutrients after 12 months were indeed significantly higher in NUTRITION compared to both baseline and PLACEBO, indicating that the phased intervention strategy was feasible and overall compliance was good.

Trends towards weight gain in NUTRITION and weight loss in PLACEBO after 12 months led to a significant between-group difference in total body weight. A tendency to lose weight in PLACEBO was also found after 12 months in a trial focussing on protein-calorie supplementation by Weekes et al. [41]. Changes in muscle and fat mass parallelled total weight change but were not significant, possibly due to lack of power. Remarkably, in contrast to weight change, the subtle change in muscle mass correlated significantly with the change in PA.

Previous studies in weight-losing and muscle-wasted patients with advanced COPD showed positive short-term (1–4 months) effects of protein-calorie supplementation as adjunct to exercise training on physical capacity and muscle mass [42–44], but limited evidence is available in less advanced airflow obstruction. The INTERCOM trial, which investigated a combined nutritional and exercise intervention in the subgroup of patients with low muscle mass and reduced cycle exercise capacity, also showed positive effects on muscle mass and physical capacity in less advanced COPD patients with low muscle mass [14]. However, it could not disentangle the relative contributions of the exercise and nutritional interventions to physical performance, because the muscle-wasted control group only received usual care. In the 20-month maintenance phase of the INTERCOM trial, physical capacity remained improved in the subgroup of treated muscle-wasted patients, but 6-min walking distance declined below baseline in those receiving usual care [14]. Whereas the nutritional intervention strategy had no short- or long-term added value on physical capacity in the current trial [13], there were sustained significant positive effects on body weight, plasma nutrient levels and physical activity and a trend towards improved mental health, which could explain the difference in generic health status after follow-up.

Both EQ-5D and physical activity levels remained stable in NUTRITION and declined in PLACEBO after 12 and 15 months. These parallel changes could mean that generic health status is influenced by daily physical activity level via modulation of physiological and/or mental health.

A qualitative study in a random sample of 22 NUTRAIN participants after phase 2 identified perceived competence and autonomous motivation as determinants of a physically active lifestyle [45]. The limited between-group motivational differences could be partly explained by high levels of both intrinsic and extrinsic motivation and low levels of amotivation already apparent before counselling. Admission to PR already requires being motivated and participating in an extensive study such as this one even more so. Even so, slight changes in motivational profile may indicate some effect of the nutritional counselling.

The incremental cost-effectiveness ratio (ICER) of EUR 61,160 after phase 2 decreased to EUR 16,750 after phase 3, because of a higher gain in QALYs and lower difference in costs after phase 3. Whether an intervention is cost-effective or not depends on the threshold value of the willingness-to-pay for a QALY. In the Netherlands this threshold depends on disease burden (defined as proportional shortfall) [46]. A higher threshold applies for conditions with a higher disease burden. There are three categories, defining a low burden (proportional shortfall of 0.1–0.4 QALYs), medium (0.41–0.7) and high burden of disease (0.71–1), corresponding to thresholds of EUR 20,000, EUR 50,000, and EUR 80,000 per QALY, respectively [47]. Hence, an ICER below EUR 20,000 (after phase 3) is generally considered to be cost-effective. With an ICER of around EUR 60,000 after phase 2, the current nutritional intervention would be cost-effective for COPD patients with a disease burden of at least 0.7 QALYs. However, this estimation is associated with high uncertainty illustrated by a small proportion of bootstrap replications below a threshold value of EUR 80,000 after phase 2.

A weakness of the current study includes the unblinding after PR, which was done because it was considered unethical to continue placebo supplementation during the maintenance phase. Secondly, as already mentioned, the current study included quite a small number of patients, in line with many other comparable studies. Generalizability of the study is limited by the fact that only patients referred for PR were included. Thirdly, not achieving the sample size specified beforehand could limit our ability to detect significant results. Finally, the counselling sessions were given by nurses who lacked detailed knowledge on the domains to be improved. More detailed and tailored advice could improve adherence to a healthy lifestyle and increase health gains.

5. Conclusion

A stepwise multimodal nutritional intervention strategy, consisting of targeted nutritional supplementation and nutritional counselling, in muscle-wasted patients with moderate COPD does not enhance long-term outcome of exercise training on physical capacity but ameliorates plasma levels of the supplemented nutrients, body weight, physical activity and generic health status. This intervention increases total health care costs to a degree that might be considered acceptable for patients with a high disease burden.

Statement of authorship

Conception and design: MPMHR, SPJK, AMWJS. Drafting of manuscript: MvB, MPMHR, CvdB, AMWJS. Acquisition and analysis of data: MvB, MPMHR, CvdB, SPJK, AMWJS. Analysis and interpretation of data: MvB, MPMHR, CvdB, MB, SK. Drafting the manuscript for important intellectual content: all authors.

All authors critically revised the article and gave final approval of this version to be published.

Conflicts of interest

Mr. Van Beers, Dr. Rutten-Van Molken, Dr. Boland, Prof. Kremers and Dr. Gosker report no disclosures. Dr. Van de Bool reports grants from the Lung Foundation Netherlands and Nutricia Research during the conduct of the study. Dr. Franssen reports personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Novartis, GlaxoSmithKline and TEVA outside the submitted work. Dr. Van Helvoort reports a grant for this study as it was financially supported by a public-private consortium of Maastricht University/NUTRIM, CIRO+ BV Horn, Nutricia Research and the Lung Foundation Netherlands (grant 3.4.09.003), personal fees as employee at Nutricia Research during the conduct of the study and personal fees as employee at Nutricia Research outside the submitted work. In addition Dr. Van Helvoorta/Nutricia has a patent WO2008NL50047 20080702 issued covering the product. Prof. Wouters reports personal fees from Nycomed, Boehringer, AstraZeneca, GSK, Novartis and Chiesi. Prof. Schols reports grants from Nutricia Advanced Medical Nutrition.

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writing the report, and the decision to submit the article for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2019.03.001.

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