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Effect of targeted nutrient supplementation on physical activity and health-related quality of life in COPD: study protocol for the randomised controlled NUTRECOVER trial

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ABSTRACT

Introduction Physical and mental health are often affected in chronic obstructive pulmonary disease (COPD) adversely affecting disease course and quality of life. Abnormalities in whole body and cellular energy metabolism, dietary and plasma nutrient status and intestinal permeability have been well established in these patients as systemic determinants of functional decline and underexplored treatable traits. The aim of this study is to investigate the efficacy of 1 year targeted nutrient supplementation on physical activity level and health-related quality of life in patients with COPD.

Methods and analysis This study is a single-centre randomised, placebo-controlled, double-blind trial in 166 patients with COPD recruited from multiple hospitals in the Netherlands. The intervention group will receive a multinutrient supplement, including vitamin D, tryptophan, long-chain polyunsaturated fatty acids and prebiotic dietary fibres as main components (94 kCal per daily dose). The control group will receive an isocaloric isonitrogenous placebo. Both groups will ingest one portion per day for at least 12 months and will additionally receive counselling on healthy lifestyle and medical adherence over the course of the study. Coprimary outcomes are physical activity assessed by triaxial accelerometry and health-related quality of life measured by the EuroQol-5 dimensions questionnaire. Secondary outcomes are cognitive function, psychological well-being, physical performance, patient-reported outcomes and the metabolic profile assessed by body composition, systemic inflammation, plasma nutrient levels, intestinal integrity and microbiome composition. Outcomes will be measured at baseline and after 12 months of supplementation. In case patients are hospitalised for a COPD exacerbation, a subset outcome panel will be measured during a 4-week recovery period after hospitalisation.

Ethics and dissemination This study was approved by the local Ethics Committee of Maastricht University. Subjects will be included after written informed consent is provided. Study outcomes will be disseminated through presentations at (inter)national conferences and through peer-reviewed journals.

Trial registration NCT03807310.

Strengths and limitations of this study

- A double-blind, randomised, placebo-controlled clinical trial investigating the effect of a novel nutritional intervention product relative to placebo on objective and subjective health status in patients with chronic obstructive pulmonary disease (COPD).
- The study design resembles a real-life setting.
- Next to investigating overall efficacy, the study design allows additional insight in the relative efficacy of the nutritional intervention in clinically stable disease as well as in response to acute disease flare-ups.
- The study product is a newly developed nutritional supplement targeting nutrient status and metabolic alterations in COPD.
- The study population targets patients with moderate to very severe COPD; inclusion, long-term compliance and outcome assessment may be challenging.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterised by persistent airflow limitation resulting from loss and remodelling of the airways.[1] During the course of the disease, patients with COPD experience periods of acute worsening of respiratory symptoms called exacerbations. During severe COPD exacerbations (requiring hospitalisation) disease-related detrimental factors such as systemic inflammation, hypoxia, physical inactivity, malnutrition and treatment with

glucocorticoids and antibiotics, converge and intensify.[2] Patients with frequent exacerbations constitute a specific disease phenotype with a worse prognosis, specifically a faster decline in lung function and muscle function, a greater worsening of health status and a substantial reduction in daily physical activity.[3–6] In turn, physical inactivity drives further physical impairments, thereby increases the risk of recurrent exacerbations, leading to a vicious cycle of deterioration.[6] It is this circle that has to be broken and adapting a more healthy lifestyle may help achieving this. Adapting a healthier lifestyle, however, is not always easy and may need additional support, especially in the affected health domains.

Symptoms of dyspnoea and fatigue in patients with COPD often affect their lifestyle. Alongside with disease exacerbations and malnutrition, a sedentary lifestyle contributes to extrapulmonary manifestations including depression, cognitive decline loss of muscle mass and function and gastrointestinal (GI) problems,[7–11] causing a vicious cycle towards physical inactivity. Overall high percentages of impaired cognitive function (25%) and depression (27%) have been observed in patients with COPD[12–14] and are negatively influenced by chronic stress and systemic inflammation.[15 16] The risk of developing cognitive dysfunction or depression is even further increased in advanced disease stages.[17 18] Skeletal muscle weakness is another well-established extrapulmonary manifestation of COPD resulting from loss of muscle mass and a decreased muscle oxidative phenotype.[19] The latter is characterised by a muscle fibre type shift from oxidative type I towards more glycolytic type II fibres and decreased expression of oxidative enzymes and regulatory proteins (eg, peroxisome proliferator-activated receptors and their coactivator 1α (PGC-1α)),[20] which render the skeletal muscle more susceptible to fatigue.[19 20] Systemic inflammation and physical inactivity have also been identified as determinants of muscle mass loss in COPD.[20–22] During an exacerbation, enhanced systemic inflammation and physical inactivity lead to acute muscle wasting, which may not be fully restored during recovery as there is evidence for an impaired regenerative potential in these patients.[6] Disturbances of intestinal integrity manifested by increased GI permeability and alterations in intestinal fatty acid-binding protein (IFABP) have also been reported in COPD.[11] These disturbances are not only observed in stable COPD, but also during hospitalisation for a COPD exacerbation.[23] Moreover, several factors associated with COPD, including age, gender, smoking, use of corticosteroids and antibiotics, body mass index and diet, are known to cause dysbiosis in the gut microbiome.[24] However, up till now no published studies of the COPD gut microbiome are available.

The extrapulmonary manifestations in COPD are linked by the cross-talk between the gut–muscle–brain axis which includes the vagus nerve, gut hormone signalling, the immune system, serotonin and tryptophan metabolism and microbial metabolites such as short-chain fatty acids.[25] All routes might be disturbed in patients with COPD, but especially serotonin and tryptophan metabolism has recently been shown to be impaired in patients with COPD leading to unfavourable higher kynurenine/tryptophan ratios in the circulation.[26 27] By modulating tryptophan availability, the microbiota can regulate the kynurenine pathway decreasing plasma kynurenine levels. In muscle, kynurenine can also be metabolised and cleared by kynurenine aminotransferases that are regulated by PGC-1α. Interestingly, a recent study of our group showed reduced expression levels of these aminotransferases in skeletal muscle of patients with COPD, which might explain the elevated plasma kynurenine levels.[27] Impairments in the kynurenine pathway have been linked to anxiety, depression and cognitive decline.[28]

Extrapulmonary manifestations as well as impairments in the cross-talk between these extrapulmonary organs could adversely affect daily physical activity level and quality of life,[29] accelerating the vicious cycle towards physical inactivity and deterioration of physical and mental status. Interventions facilitating a more physically active lifestyle in patients with COPD are therefore needed. For instance, physical activity coaching interventions may enhance physical activity levels in patients with COPD.[30] However, current pulmonary rehabilitation strategies mainly focus on improving physical performance by exercise training and counselling targeting respiratory and skeletal muscle function,[31] but behavioural translation of improved physical performance to a more active lifestyle in COPD has been disappointing.[32–35] Therefore, additional interventions need to be investigated.

Nutritional supplementation targeting impairments of skeletal muscle and gut, by preventing or restoring disease-specific deficiencies in patients with COPD and modulation of the function of the gut–brain axis, might be beneficial in patients with COPD. As systematically summarised in table 1, omega-3 polyunsaturated fatty acids (N-3 PUFAs), tryptophan, vitamin D and nutritional fibres are particularly interesting nutritional components to explore. Intake of these components is generally low in patients with COPD, and we hypothesise that supplementation of these nutrients has positive effects on different pathways of the gut–muscle–brain axis which may jointly facilitate adaptation to a more physically active lifestyle and improved health status. To minimise risk of other nutritional deficiencies and to ensure presence of essential cofactors, supportive micronutrients are provided together with these core ingredients in the supplement.

We hypothesise that this newly developed multinutrient product facilitates maintenance of a more active lifestyle in patients with COPD and improves objective and subjective physical and mental health status relative to placebo. Therefore, the primary aim of this study is to investigate the effect of 1 year targeted nutrient supplementation compared with placebo supplementation on daily physical activity level as well as general health status in patients with COPD. Secondary aims are to investigate the effect of targeted nutrient supplementation on potential mediators: cognitive function, psychological well-being, physical

Table 1 Rationale for the core components to be included in the multimodal nutritional intervention

Component	Proposed effects and underlying mechanisms	Intake, status and supplementation in COPD
N-3 PUFAs	*Proposed effect:* lowers the risk on depression, improves cognitive function, muscle function and muscle mass as well as mitochondrial function.[75–78] *Possible underlying mechanisms:* ► Substrate inhibition of proinflammatory prostaglandin E2[79] and four series leukotrienes EPA and DHA give rise to resolvins and lipid related signalling molecules such as protectins.[80] ► N-3 PUFAs are natural ligands for PPAR gamma that attenuates NF-kB activation and inflammatory gene expression and NF-kB activation reducing systematic inflammation.[81 82] ► Altering membrane lipid composition[83] and increasing membrane fluidity which facilitate the activation of receptors, eg, adenosine A2A and dopamine D2 receptors in the brain.[84] ► Decreasing indoleamine-2,3-dioxigenase expression and increasing hippocampal serotonin, a neurotransmitter in the central and enteric nervous system.[85] ► Stimulating skeletal muscle anabolism via the Akt-mTOR-p70S6K pathway.[86] ► Stimulating muscle oxidative metabolism and boosting mitochondrial function.[78]	*Intake and status in COPD:* ► Dietary intake of PUFAs is generally low.[87–89] ► High intake is positively associated with lung function.[90] ► Blood levels decrease in time with disease progression in patients with COPD.[71] *Supplementation in COPD:* ► As an adjunct to exercise training, PUFAs significantly enhanced improvement in exercise performance and physical activity level in COPD in an 8-week and 4 months placebo-controlled RCT, respectively.[35 91]
Tryptophan	*Proposed effect*: lowers the risk for depression, improves mood, behaviour and cognitive function.[92–94] *Possible underlying mechanisms:* ► Being a precursor of serotonin.[92–94] ► Being a precursor for melatonin which may improve sleep quality which can improve functional capacity, skeletal muscle strength, cognitive function and general QoL in COPD.[95 96] ► Being a precursor for niacin (vitamin B3) which for example is essential for mitochondrial function.[97]	*Intake and status in COPD:* ► Plasma tryptophan levels are decreased during acute exacerbations.[98] ► Circulating KYN and KYN/tryptophan ratios are elevated compared with controls and is associated with disease severity,[26] KYN clearance might be reduced in skeletal muscle tissue of patients with COPD due to reduced PPAR/PGC-1α-mediated KAT expression.[27] *Supplementation in COPD*: not available
Vitamin D	*Proposed effect:* low plasma vitamin D concentrations are associated with depressive symptoms and low muscle function.[99–101] *Possible underlying mechanisms:* ► An increased region-specific expression of vitamin D receptors in brain areas play a key role in mood regulation.[102] ► Has anti-inflammatory effects leading to neuroprotective properties.[103 104] ► Maintaining a normal calcium and phosphorus balance in skeletal muscle; low vitamin D levels reduce calcium reuptake into sarcoplasmic reticulum, impairing muscle function.[99] ► Improving mitochondrial function, dynamics and enzyme function in skeletal muscle.[100]	*Intake and status in COPD:* ► Vitamin D levels are low and deficiency is highly prevalent.[105 106] ► Deficiency is associated with COPD severity, osteoporosis, depression and lower muscle strength.[37 107–110] *Supplementation in COPD:* ► Significantly improves inspiratory muscle strength, maximal oxygen uptake and QoL in patients with COPD in a 3 months and 8 weeks placebo-controlled RCT.[111 112] ► Supplementation reduces number of acute exacerbations in patients with COPD with low vitamin D plasma levels as shown in two meta-analyses.[113 114]
Prebiotic fibres	*Proposed effect*: improve gut function.[115–117] *Possible underlying mechanisms:* ► Fibres are substrate for intestinal microbes and support their growth.[116] ► Can be converted into SCFA that support gastrointestinal integrity and fuel coloncytes.[117] ► Change gut microbial composition towards a less inflammatory profile.[115] ► A mixture of prebiotic fibre may prevent alveolar wall destruction, right ventricle hypertrophy and neutrophil infiltration into the lungs after LPS instillation in mice.[118]	*Intake and status in COPD:* ► Dietary intake is generally low.[87] ► Low fibre intake is associated with reduced measures of lung function[119] and high intake with a 30% lower risk of COPD.[120] ► Dietary intake has an inverse relationship with poor lung function and COPD risk.[119] *Supplementation in COPD:* not available

COPD, chronic obstructive pulmonary disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; KAT, kynurenine aminotransferase; KYN, kynurenine; LPS, lipopolysaccharide; NF-kB, nuclear factor kappa-light chain enhancer of activated B cells; PPARs, peroxisome proliferator-activated receptors; PUFA, polyunsaturated fatty acids; QoL, quality of life; RCT, randomised controlled trial; SCFA, short-chain fatty acids.

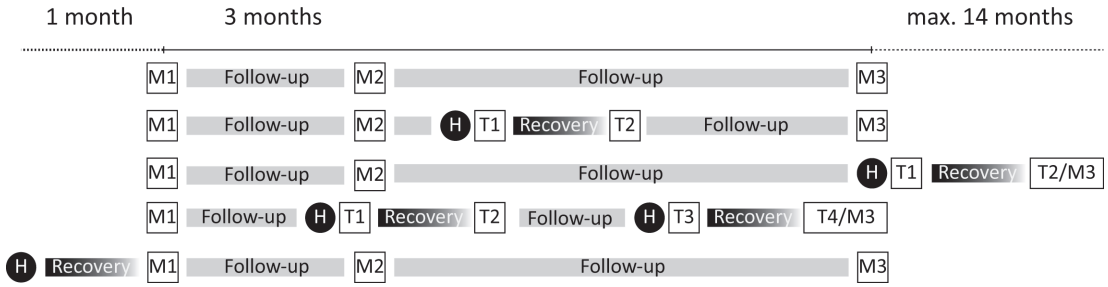

Figure 1 Study design. Measurements at baseline, after 3 months and at the end of the study are indicated as M1, M2 and M3, respectively. After a hospitalisation for a chronic obstructive pulmonary disease exacerbation (H) the recovery phase of 4 weeks will be monitored (T1 and T2). In case patients will be recruited during a hospitalisation for a COPD exacerbation, M1 will take place 4 weeks after discharge. In case the hospitalisation will be within 3 months after baseline, M2 will not take place.

performance, patient-reported outcomes and the metabolic profile assessed by body composition, systemic inflammation, plasma nutrient levels, intestinal integrity and microbiome composition in patients with COPD. As an additional explorative aim, we will investigate the relative effect of targeted nutrient supplementation during the recovery phase after hospitalisation for a COPD exacerbation.

METHODS AND ANALYSIS

Study design

The study design was developed according to the Standard Protocol Items: Recommendations for Interventional Trials 2013 recommendations.[36] In a single-centre randomised, placebo-controlled, double-blind clinical trial the active nutritional supplement will be compared with a placebo supplement in patients with COPD. Previously, after 3 months and after 12 months (extended in case of hospitalisation in the previous 4 weeks), measurements will be performed at the Maastricht University Medical Centre+ (figure 1). A 1-year follow-up period is chosen to investigate the long-term effect of nutritional supplementation in a real-life setting during which COPD exacerbations might occur. We will investigate in an explorative analysis the relative effect of targeted nutrient supplementation on clinical outcome during a 4-week recovery phase after hospitalisation for a COPD exacerbation. First of all, because disturbances in the gut–muscle–brain axis as well as specific nutrient deficiencies might be affected by severe COPD exacerbations.[3–6 37] Second, because the recovery period after severe COPD exacerbations is a completely neglected phase for nutritional interventions thus far.[2] For this, we will perform a subset panel of outcome measures within 1 week after discharge and 1 month later (recovery phase) each time a patient is hospitalised for a COPD exacerbation during the intervention period. In case the last measurement day will take place within the postexacerbation recovery phase, the intervention period will be lengthened until the end of the recovery phase, with a maximum of 2 months. See figure 1 for these different scenarios. The study has been started in October 2020 and is planned to last 3 years.

Participants

The study population will consist of patients with moderate to very severe, but medically stable, COPD according to the GOLD criteria[1] (see table 2 for detailed inclusion and exclusion criteria). Participants will be recruited via respiratory physicians from multiple hospitals in the southeast of the Netherlands or via advertisements. Potential eligible participants will receive detailed information of the study including the informed consent form (online supplemental appendix 1). Patients who are willing to participate will be screened by the researchers

Table 2 Eligibility criteria

Eligibility criteria	
Inclusion criteria	▶ Moderate to very severe COPD according to GOLD criteria (ie, GOLD stage II–IV). ▶ Medically stable (no hospital admission <4 weeks prior to the start of the study and no temporary oral steroid or antibiotics use due to a COPD exacerbation in the last 4 weeks).
Exclusion criteria	▶ Age <18 years. ▶ Allergy or intolerance to components of the study product. ▶ Other acute or unstable chronic diseases that will compromise the study outcome (eg, active cancer requiring treatments). ▶ Participation in any other study involving investigational or marketed products concomitantly or within 4 weeks prior to entry into the study. ▶ Terminal illness. ▶ Lung malignance in the previous 5 years. ▶ Diagnosis of dementia or neurodegenerative disease (eg, Alzheimer's disease, Parkinson's disease, Huntington's chorea, frontotemporal dementia) in the medical records. ▶ Recent diagnosis of cerebral conditions (<1 year, eg, cerebral infarction, haemorrhage, brain tumours, transient ischaemic attack) in the medical records. ▶ Any medical condition that significantly interferes with digestion and/or GI function (eg, short bowel syndrome, inflammatory bowel disease, gastric ulcers, gastritis, (gastro)-enteritis, GI cancer) as judged by the investigator.

COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

and study physician based on the eligibility criteria. The first participant was enrolled in October 2020.

Trial interventions

Nutritional intervention

One group will receive the targeted nutrient supplement, and one group will receive an isocaloric isonitrogenous placebo for at least 12 months. Both study products will be provided as a flavoured powder in labelled sachets that are blinded for both the participants and investigators. Participants will be randomly assigned to one of the intervention groups (see randomisation and blinding). Both supplements will be produced and supplied by Danone Nutricia Research, Utrecht, the Netherlands. The active supplement consists of 4 g proteins and free amino acids, 4 g fat (fish oil; N6/N3 ratio=0.12), 8 g carbohydrates and 6 g fibres, providing 1 g of N-3 long-chain PUFAs (600 mg eicosapentaenoic acid (EPA) and 400 mg docosahexaenoic acid (DHA)), 200 mg tryptophan, 20 µg vitamin D and 6 g of prebiotic fibres as core components (table 1). To minimise risk of other nutritional deficiencies and to ensure presence of essential cofactors, supportive micronutrients are provided at dosages present in a normal diet and below no observed adverse effect levels together with these core ingredients in the supplement. The dose of components are all within the recommendations and safety levels as provided by the European Food and Safety Authority, as published in their report of December 2017.[38] The active supplement includes a daily dose of 94 kCal. The placebo product is isocaloric and isonitrogenous where protein and free amino acid levels are compensated with L-alanine as neutral amino acid that is known to not modulate outcome parameters in patients with COPD, fish oil is replaced by vegetable oils (palm and soy oil; N6/N3 ratio=12.3) without EPA and DHA, and fibre/energy is compensated by maltodextrin. The micronutrients will not be added to the placebo powder. Each day, one sachet will be consumed after suspension in 60 mL water or any other drink. In case patients are hospitalised during the intervention period, patients will have to quit supplement ingestion temporarily until discharge in order to avoid interactions of the supplement with the medical care. The subjects will receive the nutritional supplements for a period of 2 months. New nutritional supplements will be provided at home by the investigators or sent by mail.

Healthy lifestyle counselling

Both groups will receive counselling on healthy lifestyle (in particular physical activity and smoking cessation), weight management (loss or gain) and medical adherence. Counselling is based on the Self-Determination Theory (SDT) and will be operationalised through motivational interviewing by one of the trained researchers.[39] The counselling aims at increasing self-regulation skills of the participants, as well as competence and autonomy. Briefly, at baseline subjects will be informed about the results of their physical activity level, body composition and dietary intake. Subsequently, subjects will be asked to construct specific learning goals based on their physical activity level, smoking status and weight management. Every month, one of the counsellors will contact the subjects and perform a short interview in which the subjects will be asked to recall and name the specific learning goals. Furthermore, the learning goals will be discussed and potentially adjusted using motivational interviewing. During this interview, researchers will also record any adverse events and researchers will ask the subjects the number of supplements they have left in order to check for compliance. This monthly contact will additionally give the researchers the opportunity to keep the subjects motivated for participation in this study.

Study procedures and outcomes

Table 3 gives an overview of measurements taking place at each measurement day in order to assess the study outcomes. Figure 2 provides a timeline of a baseline or end measurement day (M1 and M3). The subset of measurements included at M2, T1 and T2 will be performed in the same order as depicted in figure 2.

Primary outcomes

In line with the joint American Thoracic Society/European Respiratory Society taskforce on outcome measures in COPD, which recommends a multioutcome approach in trials with COPD, this study includes both daily physical activity level and general health status as coprimary outcomes.[40] Both primary outcomes will be measured on each measurement day (table 3). Physical activity level will be measured using the activPAL (PAL Technologies, Glasgow, Scotland), which is capable of recording step count and physical activity pattern and intensity for a continuous period. The activPAL has been validated in patients with COPD.[41] The activPAL will be attached to the centre of the right thigh and subjects have to wear this device for 7 consecutive days, 24 hours per day. The activPal calculates total amount of steps which is one of the primary outcomes in this study. Additionally, the activPAL calculates body posture as sitting, lying, standing and stepping in hours per day, and energy expenditure in metabolic equivalent of tasks (value) using static and dynamic acceleration information,[42] which will be analysed as secondary outcomes. Following the recommendation by Demeyer *et al*, only measurements including a minimum of three completely measured days will be considered valid to be included in the analysis.[43]

General health status will be assessed by the EuroQol-5 dimensions (EQ-5D), which is a generic classification system used to characterise current health states of patients. The EQ-5D consists of five domains (mobility, self-care, usual activity, pain/discomfort, anxiety/depression) and a Visual Analogue Scale (EQ-VAS). Subjects will be asked to indicate their level of health by checking one of three levels of functioning for each domain. For the VAS, subjects draw a line from a box to the point on

Table 3 Overview of study procedures at each measurement day

Outcome	Measurement	M1	M2	T1	T2	M3
Primary outcomes						
Physical activity level	Accelerometry	X	X	X	X	X
General health status	EQ-5D*	X	X	X	X	X
Secondary outcomes						
Cognitive function						
Cognitive function	CANTAB	X		X	X	X
Psychological well-being						
Depression and anxiety	DASS-21*	X		X	X	X
Vulnerability to depression	HADS*	X		X	X	X
Level of stress	PSS*	X		X	X	X
Acute stress	SECPT	X				X
Chronic stress	Hair cortisol	X		X	X	X
Physical performance						
Lower extremity performance	SPPB	X		X	X	X
Handgrip strength	Hydraulic dynamometer	X		X	X	X
Mouth pressure	MicroRPM monitor	X		X	X	X
Exercise performance	6MWT	X				X
Body composition						
Body composition	DEXA scan	X				X
	Weight	X		X	X	X
	Length	X				X
Blood markers						
Systemic inflammation	Hs-CRP, procalcitonin, IL-6, IL-8, leukocytes	X	X	X	X	X
Nutrient levels	Vitamin E and D, PUFAs, amino acids, homocysteine	X	X	X	X	X
Patient related outcomes						
Fatigue	CIS*	X		X	X	X
Pain	Pain VAS*	X		X	X	X
Sleep quality	PSQI*	X		X	X	X
Intestinal function and gut microbiome						
Intestinal integrity	IFABP rest	X		X	X	X
	IFABP after exercise	X				X
Microbiome composition	Stool sampling (optional)	X	X			X
Other						
Lung function	Spirometry and body plethysmography	X				X
Diffusion capacity	Diffusion capacity	X				X
Impact of COPD	CAT*	X		X	X	X
COPD health status	CCQ*	X		X	X	X
Breathlessness	Modified MRC-scale*	X		X	X	X
Nutritional supplement use†	Self-report	X	X	X	X	X
Medication use	Medical records and self-report	X	X	X	X	X
Medical history	Medical records and self-report	X	X	X	X	X
Food intake	3- day food diary	X				X
Motivation	SDT*	X		X	X	X

Measurements at baseline, after 3 months and at the end of the study are indicated as M1, M2 and M3, respectively. The recovery period after a hospitalisation for a COPD exacerbation is indicated as T1 and T2.
*Questionnaire.
†Subjects will be requested to refrain from the use of nutritional supplements during the course of the study. In subjects who do not stop due to their medical condition or other arguments, frequency, dose and type of nutritional supplement are recorded.
CANTAB, Cambridge Neuropsychological Test Automated Battery; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; CIS, Checklist Individual Strength; COPD, chronic obstructive pulmonary disease; DASS-21, Depression Anxiety Stress Scale; DEXA, dual-energy X-ray absorptiometry; EQ-5D, EuroQol 5 dimensions; HADS, Hospital Anxiety and Depression Scale; Hs-CRP, high-sensitive C reactive protein; IFABP, intestinal fatty acid-binding protein; IL, interleukin; MRC, Medical Research Council; 6MWT, 6 min walking test; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale; PUFAs, poly unsaturated fatty acids; SDT, Self-Determination Theory; SECPT, Socially Evaluated Cold-Pressor Test; SPPB, short physical performance battery; VAS, Visual Analogue Scale.

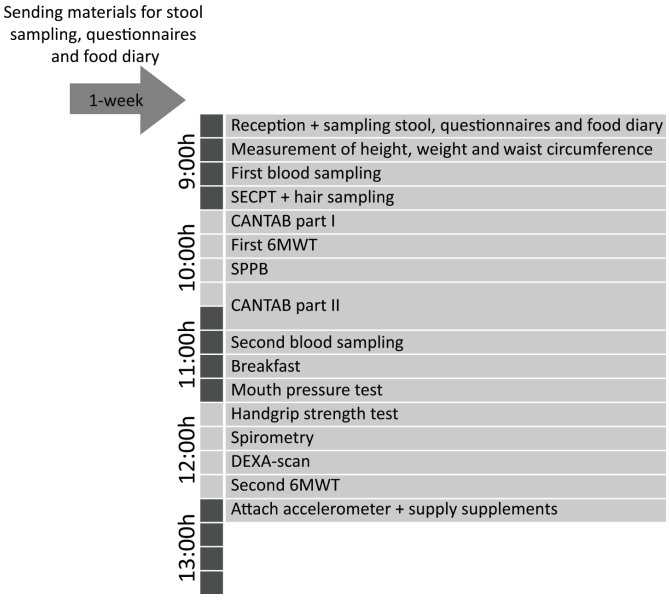

Figure 2 Timeline of measurement day. This outline provides a timeline of a measurement day at M1 and M3. During M2, T1 and T2 a selection of these measurements will be performed as described in table 3. Measurements will be performed in this order unless logistically not possible. 6MWT, 6 min walking test; CANTAB, Cambridge Neuropsychological Test Automated Battery; DEXA, dual-energy X-ray absorptiometry; SECPT, Socially Evaluated Cold-Pressor Test; SPPB, short physical performance battery.

the thermometer-like scale corresponding to their health state, 0–100 (100 is best health state).[44]

Secondary outcomes

Cognitive function

Cognitive function will be measured by the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition, Cambridge, UK) which has been widely used in a large range of clinical studies, and has been thoroughly documented, replicated and validated.[45] The CANTAB will be performed on a tablet computer under supervision of the researchers and will include the following tasks: motor screening task, reaction time task, paired associated learning, delayed matching-to-sample, spatial working memory and stop signal task.

Psychological well-being

Multiple questionnaires will be used to assess depression, anxiety and stress. The Depression Anxiety Stress Scale 21 (DASS-21) and the Hospital Anxiety and Depression Scale (HADS) will be used to assess vulnerability to depression. The DASS-21 is a clinical assessment that measures the three related states of depression, anxiety and stress.[46] It consists of 21 negative emotional symptoms and subjects will be asked how often they have experienced each symptom over the past week, on a 4-point severity/frequency scale. The HADS is a 14-item instrument designed to detect the presence and severity of mild degrees of mood disorder, anxiety and depression in hospital and community settings and outside.[47] It will allow us to measure domain-specific quality of life. The Cohen's Perceived Stress Scale, which is a measure of the degree to which situations in one's life are appraised as stressful,[48] will be used to assess the level of stress. Ten items assess how unpredictable, uncontrollable and overloaded respondents have found their lives to be over the last month. The scale also includes a number of direct queries about current stress levels.

Acute as well as chronic cognitive stress susceptibility will be measured. To assess acute stress, the Socially Evaluated Cold-Pressor Test (SECPT) following the protocol described by Schwabe *et al* will be used.[49] Briefly, the subject will immerse his or her right hand including the wrist into ice water (0°C–4°C) for a maximum of 3 min. Before and afterwards, blood pressure, heart rate and cortisol in the saliva will be measured. Furthermore, subjects will be asked to rate how stressful, painful and unpleasant this has been, on a scale from 0 ('not at all') to 100 ('very'). To assess chronic stress cortisol levels in hair samples will be measured, since this reflects the long-term impact of stress.[50] Therefore, a small piece of hair will be sampled before the SECPT to determine cortisol level in hair as a marker for long-term stress. Both saliva and hair cortisol will be determined using liquid chromatography with tandem mass spectrometry.[51]

Physical performance

To measure physical performance, the lower extremity performance will be measured by the short physical performance battery (SPPB) and the three individual types of physical manoeuvres: the balance test, the gait speed test and the chair stand test.[52] The SPPB is commonly used in older populations, but has also been shown to be a valid and simple assessment tool to measure functional impairment in COPD, independent of the severity of airflow obstruction.[53]

Muscle strength will be measured by the handgrip strength test, which has been widely used as a general indicator of frailty with predictive validity for both mortality and functional limitation.[54 55] The handgrip strength will be measured in the dominant hand using a hydraulic grip strength dynamometer.

The 6 min walking test (6MWT) will be used to measure functional exercise performance. First, a practice test will be performed as recommended by the American Thoracic Society whereupon the highest walking distance will be reported.[56] Before and after the 6MWT dyspnoea and overall fatigue using the Borg scale will be rated. The 6MWT is commonly used in clinical practice to assess impairment and functional level in patients with pulmonary disease.[56]

The MicroRPM monitor (Micro Medical/CareFusion, Basingstoke, UK), will be used to assess the maximum inspiratory and expiratory mouth pressures (MIP/MEP), as a measure for respiratory muscle strength.[57] To measure MIP, the subjects will be asked to exhale to residual volume and then perform a 'Mueller' manoeuvre, a forced inhalation against the MicroRPM with as much

effort as possible for as long as possible (minimum 2 s). To measure MEP, subjects will be asked to inhale to total lung capacity and then perform a 'Valsalva' manoeuvre, a forced exhalation against the MicroRPM with as much effort as possible for as long as possible (minimum 2 s). Both MIP and MEP procedures are repeated three times, of which the highest value is used.

Body composition

To assess whole body composition a dual energy X-ray absorptiometry (DEXA) scan will be performed. Using the DEXA scan lean mass, fat mass and bone mass can be measured at whole body level and for the extremities. Furthermore, height and weight will be measured using a wall-mounted stadiometer and a standard balance beam scale.

Systemic inflammation and nutrient levels

Blood samples (both serum and plasma) will be stored at −80°C and will be analysed after completion of the trial. Markers of systemic inflammation (such as high-sensitive C-reactive protein, procalcitonin, interleukin-6, interleukin-8 and leucocyte levels), nutrient status (such as vitamin E, vitamin D, PUFAs, amino acids (tryptophan) and homocysteine) and mechanistic markers of gut–muscle–brain cross-talk (such as kynurenine and kynurenic acid) will be determined as previously described.[27 35] The nutrient levels will be used to check for compliance.

Patient-related outcomes

The Checklist Individual Strength (CIS) will be used to assess fatigue. The CIS is a 20-item self-report questionnaire that measures several aspects of fatigue: fatigue severity, concentration, motivation and physical activity level.[58]

The VAS will be used to assess pain. In case patients experience pain in a specific part of the body, the location of the pain will be reported.

Pittsburgh Sleep Quality Index (PSQI) will be used to assess sleep quality. The PSQI is a self-report questionnaire to assess sleep quality. The questionnaire consists of 19 individual items, creating seven components that produce one global score.[59]

Intestinal integrity and gut microbiome

To evaluate the presence and the extent of small intestine injury, plasma intestinal fatty acid-binding protein (IFABP) will be determined in rest and after the 6MWT using an enzyme-linked immunosorbent assay.[11] IFABP is exclusively present in the gut, especially in the mature enterocytes of the small intestine and to a lesser extent in the colon. It rapidly diffuses through the interstitial space into the circulation on enterocyte membrane integrity loss, making it an early and sensitive marker of small intestine injury.[60] One hour after the 6MWT, IFABP will again be determined, since activities of daily living led to enterocyte damage in patients with COPD.[11]

In addition, composition of the gut microbiome will be measured in selected stool samples. Stool sampling is voluntary for each subject. Preferably, the day before the measurement day subjects will gather stool samples at home in a container and store them in a cool environment. The consistency of the stool samples will be scored using the Bristol stool form scale,[61] ranging from 1 (ie, hard lumpy) to 7 (ie, watery/liquid stools). Stool samples will be aliquoted and stored at −80°C until microbiome composition and functionality is analysed using state-of-the-art metagenome sequencing.[62]

Other study outcomes

In addition to the secondary outcomes, lung function will be measured using postbronchodilator spirometry according to the GOLD criteria.[1] Additionally, questionnaires will be used to determine disease impact on well-being and daily life,[63] COPD-specific health status[64] and breathlessness.[65] Medication use medical history and history of exacerbations will be recorded based on self-report and based on medical records. Furthermore, subjects will be asked to record everything they eat and drink for 3 entire days (3-day food diary) in order to assess the food intake. For everything they consume subjects are asked to record the time of consumption, the type of food, the brand name and a detailed description and the amount consumed and anything that was added to the food (eg, sugar, salt). Additionally, subjects underlying motivational regulations for being physically active and eating healthy will be determined using multiple SDT-based questionnaires.[66–70] In case a subject will be hospitalised for a COPD exacerbation, details of the exacerbation (eg, duration, viral/bacterial infection based on sputum and blood markers including C-reactive protein and eosinophils, blood gases) will be recorded from medical records.

Statistical analysis

Sample size calculation

The recruitment target is calculated to ensure adequate statistical power to detect a difference in the primary outcomes step count and general health status after 1 year supplementation with the active nutritional supplement compared to the placebo supplement. Both outcomes have been assessed in our previous NUTRAIN trial,[35 71] so we expect a mean difference between the intervention and placebo group of 900 steps/day (which is also considered a clinically important difference[72]) with a SD of 1790 steps/day and a mean difference in EQ-5D index score of 0.0775 with a SD of 0.153. Using a power of 80% and a significance level of 0.05, we conclude that 62 patients per group finishing the intervention will be sufficient. Based on our experiences with the NUTRAIN trial, we estimate that the drop-out rate will be 25%. Therefore, 83 patients per group will be included.

Randomisation and blinding

Participants meeting the eligibility criteria will be randomised to the active or placebo supplement by an independent researcher. A block randomisation will be

conducted to ensure equal allocation of patients in the intervention and control group. The block size will be 10, including five interventions and five controls. The independent researcher will use the minimisation method to maintain an equal distribution in age, gender, lung function and history of exacerbations of the subjects.[73 74] Briefly, the independent researcher will regularly check (after every 25 included subjects) if these factors are statistically comparable between both groups. In case of large differences, the independent researcher will influence the randomisation scheme by manually appointing future subjects to one of the groups until groups are comparable again. The independent researcher will provide the investigator with a number corresponding to a batch of sachets which the investigator will provide to the subjects. The dependent investigators as well as the subjects will be blinded throughout the study.

Data analysis and statistical methods

Data analyses will be conducted using the statistical package IBM SPSS Statistics for Windows (SPSS Inc, Chicago, Illinois, USA). Kolmogorov-Smirnov normality test will be used to evaluate normal distributions. If necessary, data will be transformed with appropriate functions to achieve normality. In normally distributed data baseline values for the two groups will be compared by the independent sample t-test. If transformation does not result in normally distributed data, non-parametric methods will be used. χ^2 analysis will be performed for categorical variables. Generally, all analyses will be performed according to the intention-to-treat (ITT) principle. Only subjects' compliant to the intervention will be included in the per protocol analysis, which will be used as a sensitivity analysis for the ITT analyses. A second per protocol analysis will be performed excluding subjects that used nutritional supplements other than the study products. Within the subset of patients who have been hospitalised for a COPD exacerbation, the effect of nutritional supplementation on the recovery phase (T1 and T2) will be investigated as an explorative analysis. To determine the effects of the nutritional supplementation on the primary, secondary and other parameters, repeated measures analysis will be used to compare mean changes between M1 and M2, M1 and M3 and between T1 and T2. Two-sided p values <0.05 will be claimed as statistically significant.

Safety assessment

Adverse events and serious adverse events will be recorded during the study. An independent data safety monitoring board (DSMB) will be assigned to perform analysis on the serious adverse events data. The DSMB will meet after 25%, 50% and 75% of the inclusion is completed or when principal investigators do striking observations that need further investigation. The DSMB will check whether serious adverse events are related to the study product and will subsequently give the principal investigators advice on the continuation of the study.

Patient and public involvement

A patient advisory panel is included in the current study and gave feedback on the study design and patient information during a face-to-face meeting that was organised by the researchers. During the study, this panel will be informed about the study progression and at the end of the study they will be involved in interpretation and dissemination of the results towards the patient population. Additionally, all individual participants will be informed about their personal results after a measurement day. After the full study has been finished, all participants will be informed about the total study results.

ETHICS AND DISSEMINATION

The study has been approved by the Medical Ethics Committee from Maastricht University Medical Centre+ (MUMC+ (NL66543.068.18/METC18-011)) and is registered at clinicaltrials.gov (NCT03807310). The study will be conducted according to the principles laid down in the Declaration of Helsinki (Brazil, October 2013). Subjects will be provided with at least 1 week to consider their participation and will be given an opportunity to ask questions before they will sign the informed consent. Subjects will be informed that they can leave the study at any time for any reason. Handling of the personal data in this study will conform to the General Data Protection Regulation. Data will be handled confidentially. To trace data of individual subjects, the study will use a subject identification code list that is linked to the data of the participating subjects. Only the principal investigators have access to this code list. The results of this study will be disseminated through presentations at national and international respiratory and nutritional conferences and through publications in peer-reviewed journals.

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Bijlage 4: Toestemmingsverklaring

Voor deelname aan het wetenschappelijk onderzoek:
Het effect van een voedingsinterventie op de dagelijkse lichamelijke activiteiten en de gezondheidstoestand van patiënten met COPD
(NUTRECOVER trial) (NL66543.068.18; versie 8 / 13/09/2021)

Ik heb de informatiebrief gelezen (Versie 6). Ook kon ik vragen stellen. Ik had genoeg tijd om te beslissen of ik meedoe. Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen of te stoppen met het onderzoek. Daarvoor hoef ik geen reden te geven.

- Ik geef toestemming voor het informeren van mijn huisarts en behandelend arts dat ik meedoe aan dit onderzoek.
- Ik geef toestemming voor het opvragen van informatie bij mijn huisarts/specialist(en) die mij behandelt voor COPD.
- Ik geef toestemming voor het verzamelen en gebruiken van mijn gegevens, bloedmonsters en lichaamsmateriaal voor de beantwoording van de onderzoeksvraag in dit onderzoek.
- Ik weet dat voor controle van het onderzoek sommige mensen toegang tot al mijn gegevens kunnen krijgen. Die mensen staan vermeld in de informatiebrief. Ik geef toestemming voor
  die inzage voor deze personen.
- Ik geef toestemming voor het informeren van mijn huisarts en/of behandelend specialist van onverwachte bevindingen die van belang (kunnen) zijn voor mijn gezondheid.
- Ik geef **wel/geen** (doorhalen wat **niet** van toepassing is) toestemming om mijn persoonsgegevens langer te bewaren en te gebruiken voor toekomstig onderzoek op het gebied van leefstijlveranderingen in COPD.
- Ik geef **wel/geen** (doorhalen wat **niet** van toepassing is) toestemming om mijn lichaamsmateriaal na afloop van dit onderzoek te bewaren. En om dit later nog voor ander onderzoek te gebruiken, zoals in de informatiebrief staat.
- Ik geef **wel/geen** (doorhalen wat **niet** van toepassing is) toestemming om mij na dit onderzoek te benaderen voor een vervolgonderzoek.
- Ik wil **wel/niet** (doorhalen wat **niet** van toepassing is) geïnformeerd worden over welke behandeling ik heb gehad/in welke groep ik zat.
- Ik wil meedoen aan dit onderzoek.

Naam proefpersoon: ……

Handtekening: …… Datum: _ _ / _ _ / _ _ _ _

In te vullen door de onderzoeker: Ik verklaar hierbij dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek. Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de proefpersoon zou kunnen beïnvloeden, dan breng ik hem/haar daarvan tijdig op de hoogte.

Naam onderzoeker: ……

Handtekening: …… Datum: _ _ / _ _ / _ _ _ _