Faster functional performance recovery after individualised nutrition therapy combined with a patient-tailored physical rehabilitation programme versus standard physiotherapy in patients with long COVID: a pilot study for a randomised, controlled single centre trial

SHORT STUDY TITLE / ACRONYM: Nutrition and LOComotoric rehabilitation in long COVID (UNLOCK)

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EXECUTIVE SUMMARY

Introduction: After COVID-19, many people experience "long COVID", a condition with ongoing symptoms that affect the functional status (such as fatigue and exercise intolerance) and problems with nutrition (such as malnutrition after hospitalisation, digestive issues, or loss of smell and taste). There is a need for multidisciplinary rehabilitation, but there is little evidence of its effectiveness. The main goal of this study was to assess the feasibility of a personalised multimodal treatment (PMT), and to prepare for a large-scale study to test the effectiveness of the PMT.

Methods: Universitair Ziekenhuis Brussel (UZ Brussel) conducted the study: "*Faster functional performance recovery after individualised nutrition therapy combined with a patient-tailored physical rehabilitation programme versus standard physiotherapy in patients with long COVID: a pilot study for a randomised, controlled single centre trial*" (*UNLOCK: Nutrition and LOComotoric rehabilitation in long COVID*), KCE-trials number: LCOV21-1306). Participants were randomly assigned to an intervention group receiving the PMT or to a control group receiving standard physiotherapy. The PMT included weekly individualised nutritional advice from a dietitian and an exercise programme with a trained physiotherapist over 12 weeks. The study focused on participant's study burden, recruitment rate and attrition rate (how many participants ended their participation before the end of the intervention period), to evaluate the feasibility of the trial. The main measure of effectiveness was the difference in functional performance, measured by the 1-minute sit-to-stand test (1-MSTS, how many times the participants can stand up starting of a sitting position in 1 minute), after 12 weeks of intervention.

Results: For this study, 65 participants with long COVID living in Belgium were recruited. Their mean age was 43 years, 64.6% were female, and had a mean BMI of 25.8 kg/m². Most participants had a mild COVID-19 infection and a mean length of long COVID symptoms of 78 weeks. Recruitment took longer than expected (16 months instead of 10 months) and the attrition was higher than expected (24.6% instead of 20%). The (expected) study burden was an important limiting factor in both recruitment and attrition. On the other hand, participants who completed the trial indicated that although the study burden was high, they were satisfied with their trial experience. The intervention-specific procedures were highly feasible: participants received a mean of 10 consultations with the dietitians and 15 physiotherapy sessions in 12 weeks. The study participants had a low functional performance at the beginning of the study, as participants performed 24 ± 8 sit-to-stand repetitions. After 12 weeks of intervention, participants in the intervention group performed an additional 4 [95% Confidence interval: 2, 5] repetitions, compared to 3 [95% CI: 0, 5] in the control group. A change of 3 additional repetitions is considered clinically important. This indicates that the functional performance improved in both groups. Based on the effects we found in this pilot study between the intervention and control group and considering a 24.6% attrition rate, we calculated a sample size of 142 individuals with long COVID for the large-scale study to assess the effectiveness of the PMT.

Discussion: The study burden was high but acceptable as indicated by the participants who completed the trial. The personalised treatment programme was feasible in the long COVID population. As a pilot study, the UNLOCK study is not powered to show treatment efficacy, but the results show promise and reinforced the need for research on the multidisciplinary management of long COVID. More information: unlock@uzbrussel.be

Inleiding: Na COVID-19 ervaren veel mensen "*long COVID*", een aandoening met aanhoudende symptomen die de functionele status beïnvloeden (zoals vermoeidheid en inspanningsintolerantie) en problemen met voeding (zoals ondervoeding na ziekenhuisopname, spijsverteringsproblemen of verlies van reuk en smaak). Er is behoefte aan multidisciplinaire revalidatie, maar er is weinig bewijs voor de effectiviteit ervan. Het hoofddoel van dit onderzoek was het beoordelen van de haalbaarheid van een gepersonaliseerde multimodale behandeling (PMB) en het voorbereiden van een grootschalig onderzoek om de effectiviteit van de PMB te testen.

Methoden: Het Universitair Ziekenhuis Brussel (UZ Brussel) voerde de studie uit: " *Faster functional performance recovery after individualised nutrition therapy combined with a patient-tailored physical rehabilitation programme versus standard physiotherapy in patients with long COVID : a pilot study for a randomised, controlled single centre trial" (UNLOCK: Nutrition and LOComotoric rehabilitation in long COVID, KCE-trials nummer: LCOV21-1306*). Deelnemers werden willekeurig toegewezen aan een interventiegroep die de PMB kreeg of aan een controlegroep die standaard kinesitherapie kreeg. De PMB bestond uit wekelijks, geïndividualiseerd voedingsadvies van een diëtist en een oefenprogramma met een getrainde kinesitherapeut gedurende 12 weken. Het onderzoek richtte zich op de studiebelasting van de deelnemers, de rekrutering en uitval (hoeveel deelnemers hun deelname beëindigden voor het einde van de interventieperiode), om te haalbaarheid van de studie evalueren. De belangrijkste maat voor effectiviteit was het verschil in functionele prestaties, gemeten met de 1-minuut zit-tot-stand-test (1-MSTS, hoe vaak de deelnemers kunnen opstaan vanuit een zittende positie in 1 minuut), na 12 weken interventie.

Resultaten: Voor deze studie werden 65 deelnemers met long COVID die in België woonden, gerekruteerd. Hun gemiddelde leeftijd was 43 jaar, 64,6% was vrouw en hun gemiddelde BMI was 25,8 kg/m². De meeste deelnemers hadden een milde COVID-19-infectie en een gemiddelde duur van *long COVID*-symptomen van 78 weken. De rekrutering duurde langer dan verwacht (16 maanden in plaats van 10 maanden) en de uitval was hoger dan verwacht (24,6% in plaats van 20%). De (verwachte) studielast was een belangrijke beperkende factor voor zowel de rekrutering als de uitval. Aan de andere kant gaven deelnemers die het onderzoek hadden voltooid aan dat ze tevreden waren met hun ervaringen, ondanks de hoge studielast. De interventie-specifieke procedures waren zeer haalbaar: de deelnemers kregen gemiddeld 10 consultaties bij de diëtisten en 15 kinesitherapiesessies in 12 weken. De deelnemers aan het onderzoek hadden een lage functionele prestatie aan het begin van het onderzoek, aangezien deelnemers 24 ± 8 zit-tot-stand herhalingen uitvoerden. Na 12 weken interventie voerden deelnemers in de interventiegroep 4 [95% Betrouwbaarheid Interval: 2, 5] extra herhalingen uit, vergeleken met 3 [95% BI: 0, 5] in de controlegroep.Een verandering van 3 extra herhalingen wordt als klinisch belangrijk beschouwd. Dit geeft aan dat de functionele prestaties in beide groepen verbeterden. Op basis van de effecten die we vonden in deze pilotstudie tussen de interventie- en controlegroep en rekening houdend met een uitvalpercentage van 24,6%, berekenden we een steekproefgrootte van 142 personen met long COVID voor een grootschalige studie om de effectiviteit van de PMB te beoordelen.

Discussie: De studielast was hoog, maar acceptabel zoals aangegeven door de deelnemers die de studie voltooiden. Het gepersonaliseerde behandelingsprogramma was haalbaar in de long COVID-populatie. Als pilotstudie is de UNLOCK-studie niet geschikt om de werkzaamheid van de behandeling aan te tonen, maar de resultaten zijn veelbelovend en versterken de behoefte aan onderzoek naar een multidisciplinaire aanpak van long COVID. Meer informatie: unlock@uzbrussel.be

Introduction : Après le COVID-19, de nombreuses personnes souffrent du "*COVID long*", un état caractérisé par des symptômes persistants qui affectent l'état fonctionnel (comme la fatigue et l'intolérance à l'effort)

et des problèmes de nutrition (comme la dénutrition après une hospitalisation, des problèmes digestifs ou la perte de l'odorat et du goût). Une réadaptation multidisciplinaire est nécessaire, mais il existe peu de preuves de son efficacité. L'objectif principal de cette étude était d'évaluer la faisabilité d'un traitement multimodal personnalisé (TMP) et de préparer une étude à grande échelle pour tester l'efficacité du PMT.

Méthodes: L'Universitair Ziekenhuis Brussel (UZ Brussel) a mené l'étude: "*Faster functional performance recovery after individualised nutrition therapy combined with a patient-tailored physical rehabilitation programme versus standard physiotherapy in patients with long COVID : a pilot study for a randomised, controlled single centre trial" (UNLOCK : Nutrition and LOComotoric rehabilitation in long COVID), KCE-trials numéro : LCOV21-1306*). Les participants ont été répartis au hasard entre un groupe d'intervention recevant le TMB et un groupe de contrôle recevant la kinésithérapie standard. Le TMB comprenait des conseils nutritionnels hebdomadaires et personnalisés de la part d'un diététicien et et un programme d'exercices avec un kinésithérapeute qualifié sur une période de 12 semaines. L'étude s'est concentrée sur la charge de travail des participants, le taux de recrutement et le taux d'attrition (combien de participants ont mis fin à leur participation avant la fin de la période d'intervention), afin d'évaluer la faisabilité de l'essai. La principale mesure d'efficacité était la différence de performance fonctionnelle, mesurée par le test assis-debout d'une minute (1-MSTS, combien de fois les participants peuvent se lever à partir d'une position assise en 1 minute), après 12 semaines d'intervention.

Résultats : Pour cette étude, 65 participants atteints de COVID long et vivant en Belgique ont été recrutés. Leur âge moyen était de 43 ans, 64,6 % étaient des femmes et leur IMC moyen était de 25,8 kg/m². La plupart des participants présentaient une infection légère du COVID-19 et la durée moyenne des symptômes de COVID long était de 78 semaines. Le recrutement a duré plus longtemps que prévu (16 mois au lieu de 10) et le taux d'abandon a été plus élevé que prévu (24,6 % au lieu de 20%). La charge d'étude (prévue) a été un facteur limitant majeur pour le recrutement et l'abandon. D'un autre côté, les participants qui ont terminé l'étude se sont déclarés satisfaits de leur expérience, malgré la charge de travail élevée. Les procédures spécifiques à l'intervention étaient très réalisables: les participants ont bénéficié en moyenne de 10 consultations avec des diététiciens et de 15 séances de kinésithérapie en 12 semaines. Les participants avaient de faibles performances fonctionnelles au début de l'étude, puisque les participants effectuaient 24 ± 8 répétitions assis-debout. Après 12 semaines d'intervention, les participantes du groupe d'intervention ont effectué 4 [95% intervalle de confiance: 2, 5] répétitions supplémentaires, contre 3 [95% IC: 0, 5] dans le groupe de contrôle.Un changement de 3 répétitions supplémentaires est considéré comme cliniquement significatif. Cela indique que les performances fonctionnelles se sont améliorées dans les deux groupes. Sur la base des effets constatés dans cette étude pilote entre le groupe d'intervention et le groupe de contrôle, et compte tenu d'un taux d'abandon de 24,6 %, nous avons calculé une taille d'échantillon de 142 personnes atteintes de COVID long pour une étude à grande échelle visant à évaluer l'efficacité du TMP.

Discussion : Le fardeau de l'étude était élevé mais acceptable, comme l'indiquent les participants qui ont terminé l'étude. Le programme de traitement personnalisé était réalisable dans la population COVID long. En tant qu'étude pilote, l'étude UNLOCK ne permet pas de démontrer l'efficacité du traitement, mais les résultats sont prometteurs et renforcent la nécessité d'une recherche sur une approche multidisciplinaire du COVID pulmonaire. Pour plus d'informations : unlock@uzbrussel.be

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LIST OF ABBREVIATIONS

1-MSTS: 1-minute sit-to-stand test

6-MWT: Six-minute walk test

BIA: Bioelectrical Impedance Analysis

BMI: Body Mass Index

CME: Commission for Medical Ethics

COVID-19: Coronavirus disease 2019

EQ-5D-5L: EuroQol Group 5 dimensions 5 levels

FFM: Fat-free mass

FM: Fat mass

HADS: Hospital Anxiety and Depression Scale

IC: Indirect Calorimetry

ICU: Intensive care unit

IPQ: Illness Perception Questionnaire

ME/CFS : Myalgic encephalomyelitis/chronic fatigue syndrome

MFI-20: Multi-dimensional Fatigue Inventory

mMRC: Modified Medical Research Council dyspnoea questionnaire

PAL: Physical Activity Level

PCFS: Post-COVID-19 functional status scale

PESE: Post-exertional symptom exacerbation

PhA: Phase angle

PMT: Personalized multimodal treatment

RCT: Randomized controlled trial

REE: Resting Energy Expenditure

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus

SPFQ: Study Participant Feedback Questionnaire

TEE: Total Energy Expenditure

WHO: World Health Organisation

WPAI: Work Productivity and Activity Impairment Questionnaire

1. INTRODUCTION

The Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) has already led to more than 775 million reported coronavirus disease 2019 (COVID-19) cases and over 7 million deaths worldwide, as of June 2024 [1]. A significant proportion of COVID-19 survivors experience post-COVID-19 condition, more popularly known as long COVID. It is defined by the World Health Organisation (WHO) as "a *condition in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually within 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis*"[2]. The literature estimates that 10-30% of non-hospitalized infected individuals, 50-70% of hospitalized individuals and 10-12% of individuals with complete vaccination develop long COVID [3-5]. Based on the modest estimate of 10% of infected individuals, roughly 77 million individuals suffer from long COVID globally. Based on a meta-analysis, there are several patient-related risk factors, such as older age, female sex, higher Body Mass Index (BMI), smoking, the presence of physical and mental comorbidities, and hospitalisation or admission in the intensive care unit (ICU) [6].

Over 100 symptoms have been linked to long COVID. The most common complaints are fatigue, headache, attention disorder ('brain fog'), hair loss and dyspnoea [7, 8]. Otherwise, persistent exercise intolerance, also referred to as post-exertional symptom exacerbation (PESE) is frequently seen [9]. These symptoms have an impact on the physical, cognitive and mental functioning and lead to reduced autonomy and health-related quality of life [10-13]. Additionally, absenteeism due to long COVID has a large economic impact, as many people with long COVID must reduce their work schedule or are unable to work, often months and even years after infection [14-16]. Besides these physical and functional symptoms, nutritional status is also an issue. During hospitalisation for COVID-19 malnutrition, cachexia, sarcopenia and high visceral adipose tissue are frequently reported [17-22]. Additionally, small percentages of people with long COVID suffer from gastro-intestinal symptoms such as nausea, vomiting, diarrhoea, or other symptoms that limit their food intake, such as loss of smell and taste, even 2 years after the SARS-CoV-2 infection [23].

The combination of low functionality, low muscle mass and excess adipose tissue should be targeted as a treatment point of engagement. The WHO guideline on the clinical management of COVID-19 recognizes that this multisystem disease may require multidisciplinary rehabilitation [24]. However, no evidence of the effectiveness of multidisciplinary rehabilitation on long COVID has yet been provided by randomized controlled trials and most recommendations from international guidance are based on expert opinion or evidence from other diseases, such as cancer, chronic obstructive pulmonary disease or myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [25-27].

Our hypothesis is that an individualized nutritional therapy, combined with individualized physical rehabilitation program may lead to a faster improvement of functional performance compared to a standard physiotherapy program in people suffering from long COVID. Before running a large randomized controlled trial (RCT), it seems necessary to perform a pilot study that assesses the feasibility and participant burden of the proposed intervention and to recruit participants for such trial.

2. SUMMARY OF THE UNLOCK PILOT STUDY PROTOCOL

Trial title	Faster functional performance recovery after individualised nutrition therapy combined with a patient-tailored physical rehabilitation programme versus standard physiotherapy in patients with long COVID: a pilot study for a randomised, controlled single centre trial
Short title	UNLOCK: Nutrition and LOComotoric rehabilitation in long COVID
Trial design	Pilot study for a randomised controlled single centre trial
Trial participants	Individuals with long COVID
Setting	Tertiary care, University Hospital Brussels
Planned sample size	66 participants
Intervention	A personal multimodal therapy combining a tailored-made physiotherapy programme and nutritional counselling/optimisation therapy
Control	Standard physiotherapy
Follow-up duration	12 weeks (± 7 days) intervention + 6 weeks (± 7 days) follow-up
Planned trial period	24 months

	Objectives
Primary	To prepare a larger scaled RCT that addresses the effectiveness of a personalized multimodal treatment (PMT) consisting of individualized nutritional therapy, combined with individualized physical rehabilitation program. This pilot offers us necessary information on the **feasibility** of the future experiment. The UNLOCK trial investigates whether a PMT is able to improve functional performance recovery faster than standard physiotherapy alone.
Secondary	A second aim is to get a better understanding of the relevant data related to the primary endpoints. This is necessary because of the lack of data in this population. Hence, a convenient sample size can be calculated.

	Endpoints
Primary	Feasibility outcomes: • Participant study burden • Recruitment rate • Attrition rate Difference in the 1-minute sit-to-stand test (e.g., how many times the participants can stand up starting of a sitting position in 1 minute) at baseline (T0) and at the end (= 12 weeks) of the intervention (T2)
Secondary	Changes in…

	• Fatigue at baseline (T0), 6 weeks ± 7 days (T1) and 12 weeks ± 7 days (T2) and 18 week (6 weeks follow-up) ± 7 days (T3) (Multi-dimensional Fatigue Inventory (MFI-20)) • Health-related quality of life at T0, T1, T2 and T3 (EuroQol Group 5 dimensions 5 levels (EQ-5D-5L)) • Functional status at T0, T1, T2 and T3 (post-COVID-19 functional status scale (PCFS)) • Work-related activities at T0, T1, T2 and T3 (Work Productivity and Activity Impairment Questionnaire (WPAI)) • Health-related mental health at T0, T1, T2 and T3 (Hospital Anxiety and Depression Scale (HADS))

Explanatory	• Sex (Male/Female)
	• Adherence
	• Compliance
	• Illness perception (Illness Perception Questionnaire (IPQ))
	• Duration of symptoms (weeks)
	• COVID-19 hospitalisation, length of hospitalisation, ICU stay and length
	• Sickness leave, length of sickness leave.
	• Physical performance at T0, T1, T2, T3 (six minute walk test and muscle strength, handgrip strength)
	• Nutrition at T0, T1, T2, T3 :
	  ○ Resting Energy Expenditure (REE)
	  ○ Feeding adequacy
	  ○ Body composition
	• Dyspnoea at T0, T1, T2, T3 (modified Medical Research Council dyspnoea scale)
	• Activities of daily living at T0, T1, T2, T3 (Barthel Index)

3. OBJECTIVES AND ENDPOINTS/OUTCOME MEASURES

The overall objective of the UNLOCK pilot trial was to prepare for a feasible, large scale randomised controlled trial (RCT) that assesses the effectiveness of a personalized multimodal treatment (PMT) compared to standard physiotherapy alone. The PMT consisted of 18 sessions of individualized physiotherapy tailored to the needs of the participant, in combination with weekly teleconsultations with a study dietitian.

To assess the effectiveness of such a PMT, during the intervention period, the participants were invited at baseline (T0), 6 weeks ± 7 days (T1) and 12 weeks ± 7 days (T2) for a study visit. They were also asked to attend a study visit 6 weeks ± 7 days (T3) after the intervention period is done (= follow-up). During the visits, several outcomes were measured. The outcomes were chosen in line with the most frequently reported symptoms. For the motivation as to why we chose the outcomes, we reference the UNLOCK protocol version 3.0, 06-Feb-2023 and the published protocol paper [28].

3.1. PRIMARY OBJECTIVE OF THE PILOT STUDY

Before conducting a large scaled RCT that addresses the effectiveness the PMT, this pilot study assessed the **feasibility** of such a PMT in the long COVID population, as well as the feasibility of the study design. To assess the **effectiveness** of this PMT, we evaluated if the PMT is able to improve the functional performance recovery participants with long COVID faster compared to standard physiotherapy alone.

3.2. SECONDARY OBJECTIVES OF THE PILOT STUDY

A second aim was to get a **better understanding of the data**, because of the heterogeneity of the long COVID population and because of the lack of RCT studies that prove the effectiveness of PMT on long COVID.

3.3. PRIMARY ENDPOINTS IN THE PILOT STUDY

3.3.1. Feasibility outcomes

To assess the feasibility of the pilot study, we tested the trial procedures and processes. This implies running through the full procedures, with the participants, to detect possible challenges and protocol deviations. Our focus in terms of feasibility were **participant study burden** and **recruitment and attrition rates**.

After the last visit (T3), participants were invited for a feedback consultation. To collect data on the participant's experience throughout the trial systematically, we used section C of the Study Participant Feedback Questionnaire (SPFQ) (TransCelerate Biopharma Inc.).

3.3.2. Effectiveness outcome

To assess the effectiveness of this PMT, we evaluated if the PMT was able to improve the **functional performance** recovery in individuals with long COVID faster compared to standard physiotherapy alone.

The primary endpoint was the difference in functional performance after 12 weeks of therapy between the intervention group (receiving PMT) and the control group (receiving standard physiotherapy). We evaluated this change using the **1-minute sit to stand test (1-MSTS)** as primary outcome.

3.3.3. Minimum criteria for advancing to the full trial

We defined the following criteria that needed to be met before moving on to the full powered RCT:

- Recruitment rate of 10 participants per month, with maximally 10 months of recruitment;
- Attrition of < 20%;
- Recruitment rate of 66% based on the percentage of the population that is eligible (90%); and based on a discussion between the members of our consortium, an expected consent rate of 80% and an expected screen failure of 10%.
- We should be able to screen 100 individuals within approximately 10 months after the start of the study
- We expect the risk of the trial to be comparable to the risk of standard medical and paramedical care.

3.4. SECONDARY ENDPOINTS IN THE PILOT STUDY

The secondary endpoints (Table *1*: Secondary endpointsTable 1) were defined based on discussions with our Patient Advisory Board and based on the available literature. The goal was to define the most frequently experienced problems and the impact of the symptoms on everyday functioning, to evaluate their changes throughout the participation in the study.

Table 1: Secondary endpoints

Endpoint Change in…	Outcome *(median, 25th-75th percentile)*
Fatigue at T0, T1, T2 and T3	Multi-dimensional Fatigue Inventory (MFI-20)
Health-related quality of life at T0, T1, T2 and T3	EuroQol Group 5 dimensions 5 levels (EQ-5D-5L)
Functional status at T0, T1, T2 and T3	post-COVID-19 functional status scale (PCFS)
Work-related activities at T0, T1, T2 and T3	Work Productivity and Activity Impairment Questionnaire (WPAI)
Health-related mental health at T0, T1, T2 and T3	Hospital Anxiety and Depression Scale (HADS)

T0: baseline; T1: 6 weeks ± 7 days; T2: 12 weeks ± 7 days (= end of intervention); T3: follow-up 6 weeks ± 7 days after end of intervention.

3.5. EXPLORATORY ENDPOINTS

Explanatory outcomes were:

- Sex (Male/Female)
- Adherence for the exercise sessions was calculated as the ratio of the number of sessions that were carried out versus the number of planned sessions.
- Compliance was calculated as the ratio of the total training intensity*duration (recorded in the logbooks) versus the prescribed total training intensity*duration, multiplied by 100
- Illness perception (Illness Perception Questionnaire (IPQ))

- Duration of symptoms (weeks)
- COVID-19 hospitalisation (Yes/No), length of hospitalisation, ICU stay and length
- Sickness leave (Yes/No), length of sickness leave.

Furthermore, we evaluated the following explanatory endpoints:

- Physical performance at T0, T1, T2, and T3: The following assessments were used to confirm the results of the 1-MSTS test.
    - **Six-minute Walk Test (6-MWT)**
    - **Muscle strength**: measured using a handheld dynamometer (MicroFET®)
    - **Handgrip strength**: using a Martin Vigorimeter
- Dyspnoea at T0, T1, T2, and T3 was evaluated by the **modified Medical Research Council (mMRC)** dyspnoea questionnaire to confirm the results of the 1-MSTS test.
- To evaluate the extent to which a person needs help to perform activities of daily living (ADL), the **Barthel Index** was used at T0, T1, T2, and T3. This outcome was used to further explain the results of the EQ-5D-5L and the PCFS questionnaires.
- Nutritional parameters were measured at T0, T1, T2, and T3: the following parameters help to explain fatigue, lack of energy or return of energy. These variables were used to check for responders/non-responders or define subgroups and their possible correlation to primary and secondary endpoints.
    - **Resting Energy Expenditure (REE)(kcal/day)**: measured by Indirect Calorimetry (IC) or in case that the IC could not be performed, the REE was defined using the best fitting formula (e.g. WHO equations for BMI < 18.5 kg/m², Harris-Benedict equation for normal- and overweight participants)
    - **Feeding adequacy**: ratio between the intake and the individual need. The feeding adequacy was calculated for calories and proteins.
        - **Individual caloric need**: REE x Physical Activity Level (PAL) = Total Energy Expenditure (TEE)
        - **Individual macronutrients needs** (carbohydrates, lipids and proteins): based on the best fitting recommendations
        - **Dietary intake:** the mean daily intake of calories (kcal/day) and macronutrients (g/kg/day for proteins and % of energy intake for carbohydates and lipids) were calculated based on a 3-day nutritional diary, using the Belgian Food Database NUBEL Pro.
    - **Body composition** outcomes were measured at T0, T1, T2, and T3 using Bioelectrical Impedance Analysis (BIA).
        - Phase angle (PhA): reactance and resistance
        - Fat mass (FM) and Fat-free mass (FFM) ware calculated based on the measured parameters. We investigated whether the FM to FFM ratio is significantly associated with the REE measured by IC.

4. METHODOLOGY OF THE PILOT STUDY

4.1. STUDY SETTING

This trial was a pragmatic, single-centre, randomized controlled pilot study with two parallel groups: control group (receiving standard physiotherapy) and the intervention group (receiving the PMT). It was set in the Universitair Ziekenhuis Brussel (UZ Brussel), a tertiary care hospital. There, the recruitment and screening of participants, and the four study visits took place at baseline (T0), 6 weeks ± 7 days of intervention (T1), 12 weeks ± 7 days (= end of intervention) (T2) and follow-up 6 weeks ± 7 days after end of intervention (T3). Additionally, all participants were invited to a feedback consultation after the end of their participation. The physiotherapy sessions took place either in the UZ Brussel or in a private practice. The nutritional counselling took place during weekly (±2 days) phone or video calls by the study dietitians.

The overview of the study is shown in *Figure* 1.

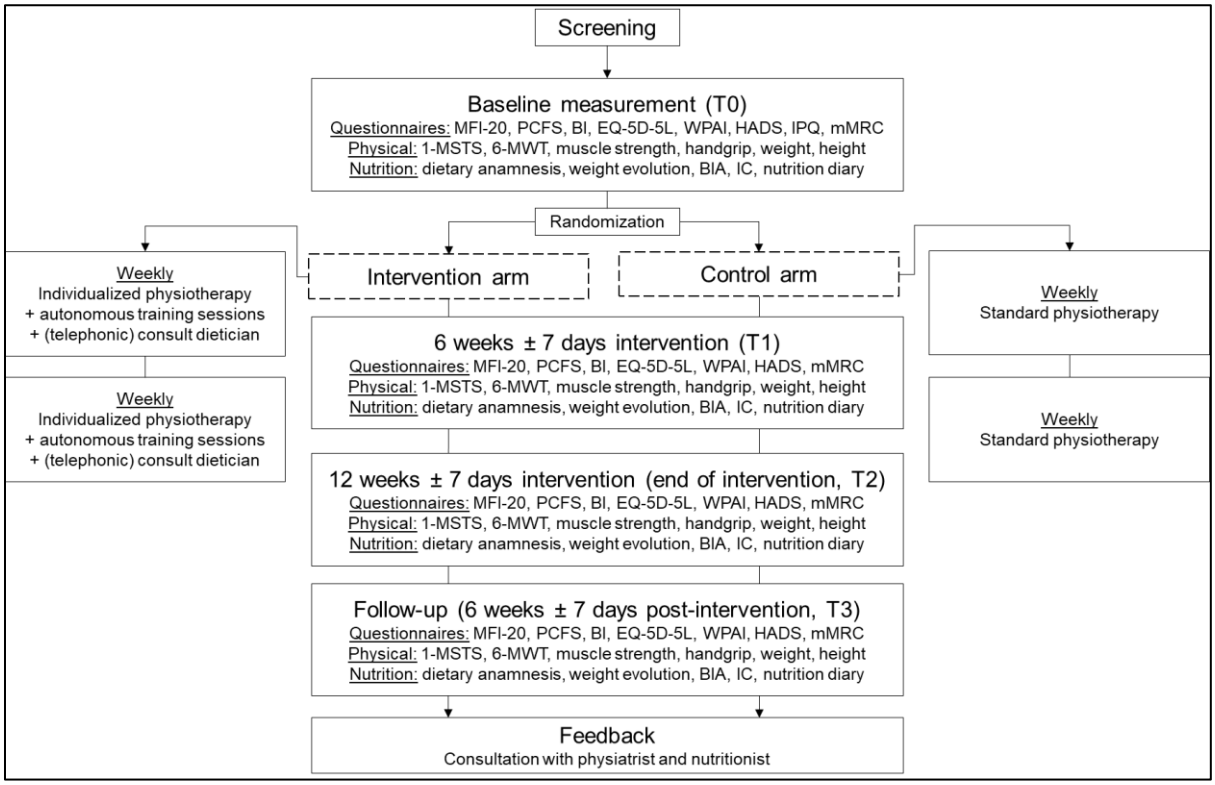


Figure 1: overview of the UNLOCK study

4.2. ELIGIBILITY CRITERIA

As we were dealing with a very heterogenic group, we limited our eligibility criteria to the minimum to include as many individuals with long COVID as possible.

Inclusion criteria:

1. Able to understand and sign written informed consent in Dutch, French or English
2. Adult (≥18 years-old)

3. Laboratory (PCR and/or serology) confirmed infection with SARS-CoV-2 or probable diagnosis based on the clinical diagnosis
4. Persisting functional difficulties and symptoms: exercise intolerance and/or fatigue and/or muscle pain beyond 12 weeks beside other COVID-related symptoms (e.g., loss of taste and/or smell)
5. Individual affiliated to a social security system

Exclusion criteria:

1. Individual currently suffers from any other disease beside long COVID that could explain the symptoms (e.g., fibromyalgia, Sjögren disease, severe anaemia...)
2. Individual is unable to undergo a rehabilitation programme due to comorbidities (e.g., major cardiovascular disease such as myocarditis or severe dementia), as decided on by the medical study team members.
3. Individual followed more than 9 sessions of physiotherapy with focus on motor and/or respiratory therapy for long COVID or any COVID-19 related diagnosis this calendar year
4. Individual with metabolic disorders or severe gastro-intestinal conditions (e.g. short bowel syndrome)
5. Individual unable to comprehend oral and/or written instructions, questionnaires in English, French or Dutch.

NOTE: When the ethics committee (EC) approved the study (27-Apr-2022), the inclusion criteria included "a laboratory confirmed infection with SARS-CoV-**2** ***less than 12 months ago***", and the exclusion criteria included "*patients* ***currently benefiting from physiotherapy sessions with a focus on motor and/or respiratory therapy for COVID or any other unrelated disease***". After the first month of screening, we saw that both criteria contributed to a low recruitment rate. These eligibility criteria were changed in the first amendment (AM-A-Amendment 1, 22-Jun-2022).

In the second amendment (AM-A-Amendment 2, 15-02-2023) we pro-actively changed the third inclusion criterion to "*Laboratory (PCR and/or serology) confirmed infection with SARS-CoV-2* ***or probable diagnosis based on the clinical diagnosis***". The reason was that a laboratory confirmation of SARS-CoV-2 infection was no longer necessary or advised in society, and a probable COVID-19 diagnosis is enough to fulfil the WHO diagnosis of long COVID [2].

4.3. PROCEDURES

4.3.1. RECRUITMENT

Leaflets and posters (approved by the EC) were spread throughout the Brussels Health Campus (Vrije Universiteit Brussel, Erasmus Hogeschool, UZ Brussel), nearby pharmacies, and participant support groups on social media by the study team. Through the *post-COVID gemeenschap* (i.e., the Flemish association for people with long COVID), potential participants were informed about the study through their social media and newsletters. The study was advertised on the UZ Brussel website, other websites and online newsletters. Additionally, the Principal Investigator made multiple appearances in traditional media (radio, television, and newspapers) where she mentioned the study. Another approved recruitment strategy was through referral by collaborating general practitioners and paramedical professionals.

All interested individuals had the opportunity to contact the research team by phone or mail, for further information about the study. At that moment, a researcher performed a telephone-based pre-screening of the participant through standardised questions to evaluate eligibility. The reason for this pre-screening was to lower the burden on the participants (less transportation and if they did not meet the eligibility criteria, they did not have to read the informed consent form (ICF) while having possible cognitive symptoms), as well as to lower the workload of the medical doctor who performs the screening consultations.

If eligible during the pre-screening, the individual was invited to a screening consultation at the department of Physical Medicine and Rehabilitation of UZ Brussel. During this consultation, there was specific attention to the presence possible cardiac or pulmonary problems, or the presence of underlying conditions that could affect the participation to the study. When necessary, the individuals were referred to other medical specialists for further investigation and/or advice.

4.3.2. INFORMED CONSENT PROCEDURE

After the pre-screening, if the individual was considered eligible, they received a digital copy of the informed consent form (ICF) through e-mail. The reason was to allow the participants to read the documents and to allow them the opportunity to ask questions before physically signing the ICF at the time of the screening consultation.

The PI or a medical doctor authorised by the PI to obtain informed consent went through the ICF with the participant, after which the participant signed the ICF. The participant always received a signed copy of the ICF.

4.3.3. WITHDRAWAL

Participation to the UNLOCK trial was voluntary. Participants remained free to refuse participation or withdraw at any time from the trial. If a participant withdrew from the trial, they were asked to provide a reason, while emphasising that answering was not mandatory and that their withdrawal would not prejudice further treatment. They could always contact the study team to obtain further information about the trial.

4.3.4. END OF PILOT INTERVENTION PERIOD

If the intervention stopped early, the reason was recorded in the participant's medical records and the eCRF whether it is due to either the participant's or clinician's decision. Possible reasons for stopping protocol treatment included:

- The participant did not wish to continue with further trial intervention
- Safety reasons
- Pregnancy
- New COVID-19 diagnosis

All participants were invited for a fifth visit at the UZ Brussel for a feedback consultation with the study dietitian, PI and medical doctor (department of Physical medicine and rehabilitation). They received a folder with their results concerning nutrition and physical performance and were given advice for further continuing their recovery. Section C of the Study Participant Feedback Questionnaire (SPFQ)

(TransCelerate Biopharma Inc.) and additional study-specific questions was used to collect data on the participant's experience throughout the trial.

4.4. DESCRIPTION OF THE INTERVENTION

All participants received a prescription for 18 sessions of physiotherapy. After the baseline assessments (T0), the participants were randomised into either the intervention group (that received the PMT) or the control group.

The participants of the control group were free to go to any physiotherapist for the management of their long COVID symptoms. In addition, they received an information leaflet with information regarding symptom-contingent pacing (i.e. usual care, conform international recommendations provided by World Physiotherapy's briefing paper 9 [29]) and general recommendations on healthy nutrition. Participants were also asked to keep track of their training sessions through an exercise and food diary, and if they made any dietary modifications.

The PMT consisted of a combination of nutritional counselling (see 4.4.1) and a physical training program (see 4.4.2). The PMT presented here considered evidence- and practice-based elements such as individual symptom-contingent pacing, self-management, and home-based functional training, and was reviewed by the patient representative. The rationale for not including a separate study arm which would allow us to investigate the contribution of the nutrition component, was based on feasibility issues as well as to respond to the cry-out and sense of urgency reported by the long COVID community.

4.4.1. Personalised nutritional counselling and nutritional optimisation

The assessor during the study visits was a registered dietitian who performed a nutritional anamnesis based on standard dietetic practice to assess the usual intake and usual eating patterns of all participants. Additionally, the BMI and weight evolution since the initial COVID-19 infection and/or in the last 3–6 months were assessed. Additionally, all participants completed a 3-day food diary before each study visit, which the registered study dietitians analysed using the Belgian Food Composition Database Nubel PRO.

In the intervention group, the study dietitians held weekly tele-consultations with the participants between baseline and T2 (= the end of the intervention period). The goal of this tele-consultation was to perform a low-threshold intervention with proven benefit and feasibility, validated in our former trial [25]. The focus of the individual nutritional therapy was to match energy and protein intake with the individualized needs, to support the physical rehabilitation and the maintenance of increase of muscle mass. Additionally, the dietitians focused on the nutritional guidelines from the Belgian High Health Council to ensure a healthy, evidence-based approach [30].

The caloric target was defined by the Resting Energy Expenditure (REE) in kcal/day measured with indirect calorimetry (Q-NRG™ Metabolic Monitor, COSMED) multiplied by a physical activity level (PAL) [31]. In case that weight loss or weight gain was indicated and compatible with the other treatment goals (e.g. combat fatigue), the caloric target was adapted accordingly. For protein, 0.83 g/kg bodyweight was used, unless a higher protein need was recommended due to specific pathology or in case of sarcopenia. Carbohydrate, fatty acids and fibre needs were defined as 50–55% of the energy requirements (En%), 30–35 En% and 3 En% respectively [30]. Any other nutritional concerns, such as

food intolerances or gastro-intestinal conditions, were taken into account. As this was a pragmatic trial, the dietitians used any evidence-based tools that they would use in usual, individualised care.

4.4.2. Personalised physical exercise program

The participants of the intervention group were asked to go to specifically trained physiotherapists for the management of their long COVID symptoms. The study team members from the Rehabilitation Research group form the Vrije Universiteit Brussel coordinated the training of the study physiotherapists. The training of the physiotherapists, based on the information provided by World Physiotherapy's briefing paper 9 [29], took place on the VUB campus. The various aspects of long COVID rehabilitation were carefully explained, and questions after the presentation were answered. At a later stage, when more physiotherapists- scattered all over Belgium- joined the study, and face-to-face training no longer seemed practically feasible, a professional online training was created with the help of audio-visual staff at the VUB. New therapists were asked to watch the training video, after which they had an (online or tele-) consultation with the research team physiotherapists to clear up any ambiguities. After the training, "booster sessions" were then organised on a regular basis for all therapists involved, where discussions were held on the basis of fictitious cases to test and, if necessary, refine the knowledge of the training.

The participants trained a maximum of two to three times a week for 12 weeks. A trained physiotherapist supervised maximally 18 sessions. The goal was to teach the participants to independently perform the program as well as to increase the training load based on individual assessments and, and most importantly: perceived symptoms. The program consisted of different progressive phases, including preparation for return to exercise (breathing and stretching), low-intensity activity, moderate-intensity analytical and functional exercises and return to pre-COVID activity regime. A **symptom-titrated pacing strategy** was implemented to account for PESE. As recommended by World Physiotherapy, people with PESE was identified by asking about their symptoms and the impact of physical, cognitive and social activities on symptoms 12 h or longer after exertion. A 5-item questionnaire, i.e., a subscale of the De Paul Symptom Questionnaire was used to assess PESE. If symptom exacerbation was present, symptom stabilization was of prime importance. Thus, symptom-contingent pacing [32] was used to engage in activities guided by perceived symptom levels to avoid worsening symptoms, conserve energy, and enable participation in meaningful activities.

Therefore, the focus was energy conservation and balancing activities with rest to avoid further exacerbation of symptoms (phase 1: breathing and stretching exercises). Subsequently, moving to next stages in the exercise program was based on measures of perceived exertion and a visual analogue scale for symptoms. During the program, the professionals involved with participants in the intervention group were equipped with a documentation map. It contained information, materials, formats, and exercises, including quick sheets with do’s and don’ts during training, motivation cards for goalsetting and evaluation, log with evaluative and motivational questions for the participant regarding the intensity, feasibility, pleasantness and training progress of the trainings/program.

4.5. DATA COLLECTION

For this study, an electronic CRF (eCRF) was created on Castor EDC to collect information regarding the participants, the study interventions, the results of assessments and adverse events.

4.5.1. Screening consultation and informed consent

For all participants, the medical doctor collected the following data after the informed consent procedure in the medical file and/or the eCRF:

- Date and time when the participant first received the ICF (medical file and eCRF);
- Version and date and time of signature of the ICF (medical file and eCRF);
- Sex (eCRF);
- Standard system anamnesis (cardiac, respiratory, abdominal, other medical history) (medical file);
- Medication (medical file, eCRF);
- Functional performance (medical file);
- Social status (medical file);
- Smoking and alcohol habits (medical file, eCRF);
- Standard clinical examination (medical file);
- Get Active Questionnaire (survey in eCRF);
- Alternative diagnoses (Yes/No) (eCRF);
- Inability to undergo a rehabilitation program (Yes/No) (eCRF);
- Ongoing physiotherapy (Yes/No) (eCRF);
- Metabolic disorders (Yes/No) (eCRF);
- COVID-19 related Hospitalization and ICU stay (and if so, length of stay) (eCRF);
- COVID-19 related Sickness leave (and if so, length of leave) (eCRF);
- Return to work (if applicable) (eCRF).

4.5.2. Study visits

For each study visit, the eCRF contained a field to indicate whether an assessment was performed or not, the date of the assessment, and the name of the assessor. In case the assessment was not performed, the reason why not was collected. Data from the following assessments will was collected during the study visits:

Questionnaires:

- Multidimensional Fatigue Inventory (MFI-20)
- Post-COVID-19 Functional Status questionnaire (PCFS)
- Barthel Index (BI)
- EuroQol five-dimensional, five-level version (EQ-5D-5L)
- Work Productivity and Activity Impairment (WPAI)
- Hospital Anxiety and Depression Scale (HADS)
- Illness Perception Questionnaire (IPQ): only at T0
- Modified Medical Research Council Dyspnoea Scale (mMRC)
- If the participant needed help with the questionnaires, and which ones (if applicable)

Physical assessments:

- 1-minute sit to stand test (1-MSTS)
- 6-minute walking test (6-MWT), saturation and pulse

- Handgrip strength (bilateral)
- Muscle strength (bilateral shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, ankle dorsiflexion)
- Weight (kg)
- Height (cm)

Nutritional assessments:

- Nutritional diary analysis based on a three-day nutritional diary (average kcal, protein (g), fat (g) and carbohydrate (g) intake)
- Resting Energy Expenditure (measured by Indirect Calorimetry, IC) (kcal)
- Physical Activity Level (PAL)
- Bioelectrical impedance analysis (BIA) (Rz, Xc, PhA, FM (kg), FMM (kg))

4.5.3. Nutrition and rehabilitation

Both the intervention and the control group were asked to keep an exercise diary for 12 weeks. The study team provided the diaries. In these diaries, the following data were collected: date, what kind of physiotherapy/exercise (supervised or autonomous), type of exercise/activity (free text), intensity (0-10), duration (minutes), if the participant experienced PESE/fatigue (Yes/No).

Both the intervention and the control group were asked to keep a three-day nutritional diary before each study visit. A study dietician collected the results from the nutritional analysis in the eCRF. Furthermore, the intervention group received weekly nutritional counselling. To assess adherence, the study dieticians collected the date of the counselling in the eCRF. The initials of the dietician who performed the counselling and the advice given (standard note) were also collected in the eCRF.

4.5.4. Data collection for the feasibility study

Extra data were collected to assess the feasibility of the study. Our focus in terms of feasibility were participant study burden and recruitment and attrition rates.

In terms of recruitment data, the following were collected during the pre-screening: ID code (to avoid the collection of personal data), date of pre-screening, fulfils eligibility criteria (Yes/No), reason for exclusion if the individual did not fulfil the criteria, recruitment strategy (whenever possible).

As mentioned in 4.3.3, if a participant withdrew from the study, they were asked to provide their reasons for prematurely ending their participation. This was used to explain the attrition rate and provide more information on the study burden.

After the last visit participants were be invited for a feedback consultation. To collect data on the participant's experience throughout the trial systematically, we used section C of the Study Participant Feedback Questionnaire (SPFQ) (TransCelerate Biopharma Inc.).

4.6. REPORTING OF ADVERSE EVENTS

Due to the low risk of the intervention, we did not foresee any specific (serious) adverse events (AE). The fact that the participants may experience sore muscle (delayed onset muscle soreness) or post-exertional malaise were not seen as an AE. This because the first is normal to expect when a

(deconditioned) individual starts physical exercise. The latter because it is inherent to long COVID. The following events were of special interest:

- AE: tendinopathy or muscle sprain and falls during exercise
- SAE: tendon or muscle rupture. Fractures as a consequence of a fall or when viewed as insufficiency fractures

5. STUDY RESULTS

5.1. RECRUITMENT

5.1.1. Recruitment strategies

Despite a great number of individuals with long COVID and a variety of recruitment strategies, recruitment was slower than expected. In total 146 individuals contacted the study site between 23-May-2022 and 21-Sep-2023, meaning that recruitment took 16 months, instead of the anticipated 10 months.

The largest proportion of candidates (38 individuals or 26%) was referred by other medical doctors within UZ Brussel. This was not one of the predefined recruitment strategies, as described in 4.3.1, although these doctors could have been motivated either by the flyers that were distributed throughout the campus or by the information available on the UZ Brussel website. Referrals by medical doctors within UZ Brussel remained constant throughout the entire recruitment period. When the recruitment rate stagnated, mentions in the media by prof. dr. De Waele were most successful, compared to the other strategies (see Table 2), leading to rise in applications.

Table 2: Candidates for participation to the study per recruitment strategy

	Individuals per recruitment strategy
Referral by medical doctors within UZ Brussel	38 *(26%)*
Mentions of the trial in media	29 *(20%)*
Mentions of the trial on websites	17 *(12%)*
Social media	13 *(9%)*
Referral by GP	10 *(7%)*
Flyers	8 *(5%)*
Referral by paramedical professionals	7 *(5%)*
Referral by other participants	2 *(1%)*
Referral by another research team	2 *(1%)*
Not specified	20 *(14%)*

5.1.2. Recruitment of participants

Of the 146 individuals who contacted the study team, 141 received a pre-screening based on the eligibility criteria and five were lost to contact before the pre-screening could take place. Of the 141 pre-screened individuals, 81 (57%) passed and 60 (43%) failed. Table 3 shows the pre-screening results throughout the duration of the study, as the eligibility criteria were adjusted after both amendments (see 4.2). The most common reason for a negative pre-screening was “not interested due to distance or expected time commitment” (18 individuals). The most common anticipated issue was the frequent (every 6 weeks) study visits in UZ Brussel.

Table 3: Pre-screening results and reasons for pre-screening fail

	Between EC approval and AM-A-Amendment 1	Between AM-A-Amendment 1 and AM-A-Amendment 2	Between AM-A-Amendment 2 and end of recruitment	Total pre-screened
Individuals pre-screened	19	73 76*	49	141*
Pre-screening fail	14 *(74%)*	35 *(46%*)*	14 *(29%)*	60 *(43%*)*
Reasons for pre-screening fail (multiple reasons were possible)				
Not interested due to distance or time commitment	0	10	8	18
Alternative diagnosis	2	8	3	13
> 9 sessions of physiotherapy		9	2	11
Already did physiotherapy	8**			8**
No symptoms such as fatigue, muscle pain, exercise intolerance	0	0	1	1
Initial infection > 12 months ago	4**			4**
No laboratory confirmation of SARS-CoV-2 infection	1	7		8
Language (other than Dutch, French or English)	0	1	0	1
No social security in Belgium	0	0	0	0

** After AM-A-Amendment 1, 22-Jun-2022, three individuals received an additional pre-screening if they were previously excluded from the study based on either of the changed eligibility criteria. ** one participant was excluded because of both criteria.*

As mentioned in 4.2, after ethics committee approval, the inclusion criteria were strict, including "*a laboratory confirmed infection with SARS-CoV-2 less than 12 months ago*", and the exclusion criteria included "*patients currently benefiting from physiotherapy sessions with a focus on motor and/or respiratory therapy for COVID or any other unrelated disease*". Of the first 14 individuals who were pre-screened, three had long COVID symptoms > 12 months after the initial infection, seven had already followed at least one session of physiotherapy that calendar year, and one individual fulfilled both of those exclusion criteria, meaning that 11 out of the 14 exclusions (79%) were due to only two criteria. To prevent low recruitment rate because of these reasons, the eligibility criteria were changed in the first amendment (AM-A-Amendment 1). In the second amendment (AM-A-Amendment 2) we pro-actively changed the inclusion criterion to: "*Laboratory (PCR and/or serology) confirmed infection with SARS-CoV-2* ***or probable diagnosis based on the clinical diagnosis***", as the laboratory confirmation of a SARS-CoV-2 infection was no longer necessary or advised in society and a probable diagnosis is enough to fulfil the WHO criteria for long COVID.

Of the 81 individuals that passed the pre-screening, eight individuals failed to attend the screening consultation. Of the remaining 73 individuals, five chose not to participate after the consultation, two were referred to the cardiologist and could not participate and one was falsely positively pre-screened (the individual did not suffer from functional symptoms such as fatigue or PESE, but had mostly cognitive symptoms). Additionally, because the recruitment had already taken longer than expected, the recruitment was stopped after 65 participants had enrolled in the study, instead of the 66 participants that were anticipated.

The complete recruitment flowchart is shown in Figure 2.

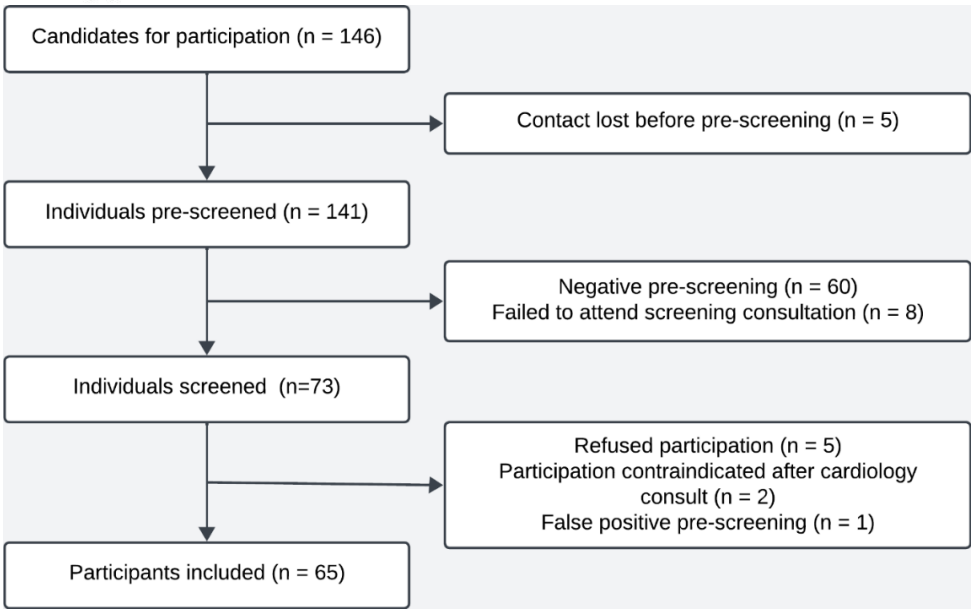


Figure 2: Recruitment flowchart

5.2. DESCRIPTION OF THE STUDY POPULATION AT BASELINE

The baseline characteristics of the study population are presented in

Table 4. The mean age was 43 ± 10 years, 64.6% was female, mean BMI was 25.8 ± 4.1 kg/m². The majority of participants had a mild COVID-19 infection, 9.2% was hospitalised during the acute infection, with an average hospitalisation length of 16 ± 18 days (range: 3 – 46 days). Of the six participants who were hospitalised (9.2%), two were admitted to the ICU (3.1% of the total sample). These participants spent respectively 9 and 31 days in the ICU. Based on the literature, the current sample fits the expected profile of the long COVID population.

The duration of long COVID symptoms was calculated as the amount of weeks between the start of the symptoms (usually corresponding with the start of the COVID-19 symptoms), and the date of the baseline study visit. In our sample, the duration of long COVID symptoms ranged from 14 to 178 weeks with a mean of 78 ± 43 weeks.

Table 4: Baseline characteristics of the study population

	Total	**CG**	**IG**
	n = 65	**n = 33**	**n = 32**
Age (years) (mean ± SD)	43 ±10	44 ± 11	43 ± 11
Sex (% female)	64.6	63.6	65.6
Smoking (% yes)	4.6	9.1	0.0
Hospitalisation (% yes)	9.2	9.1	9.4
Length of hospitalisation (days) (mean ± SD)	16 ± 18	19 ± 24	13 ± 15
ICU admission (% yes)	3.1	3.0	3.1
Length of ICU stay (days) (mean ± SD)	20 ± 16	31 ± 0	9.0 ± 0
Long COVID duration (weeks) (mean ± SD)	78 ± 43	81 ± 44	75 ± 42
BMI (kg/m²) (mean ± SD)	25.8 ± 4.1	26.0 ± 3.9	25.5 ± 4.3

BMI: Body Mass Index, ICU: intensive care unit, CG: control group, IG: intervention group, SD: standard deviation

5.3. SAFETY REPORTING

One SAE event was reported during the UNLOCK study: a participant suffered from non-epileptic myoclonia during the six-minute walking test at T1. It was deemed as a "medically significant event" as the participant was taken to the emergency department. The participant was discharged the same day in stable condition. The condition was thoroughly investigated by a medical team in the past, and concluded to be related to the long COVID diagnosis. Therefore, causality between the study intervention and the reported event was not suspected and the participant continued with the trial.

Based on the low number of (S)AEs, we conclude that the risk of the trial and the intervention is comparable to that of standard medical and paramedical care, as expected.

5.4. OUTCOME PARAMETERS

5.4.1. Feasibility outcomes

The focus of the UNLOCK study in terms of feasibility was to assess participant study burden, recruitment and attrition rates.

Study burden

Study burden was evaluated using the Study Participant Feedback Questionnaire (SPFQ) version 1.0 - section C. Statements C4 and C5 are of special interest to assess the feasibility of the study (see Figure 3). Of the 65 participants that started the trial, 44 participants (68%) completed the SPFQ at the end of their participation. 43 of them completed the trial and one had to stop prematurely due to a new COVID-19 diagnosis.

Both the intervention group and the control group report a similar experience. The majority of participants (74% in the control group, 72% in the intervention group) strongly agreed with statement C4: "Overall, I was satisfied with my trial experience". Fifty-eight percent of the control group and 48% of the intervention group stated that compared to when the trial started, the overall commitment required was similar to what they expected (C5). Thirty-two percent of the intervention group stated that the commitment what somewhat more than expected and 16% stated that it was much more than expected (compared to 26% and 11% respectively in the control group). **Based on these results, we conclude that the study burden was acceptable.** However, these results are possibly biased, as 32.3% of all participants, and none of the participants who withdrew from the trial completed the SPFQ.

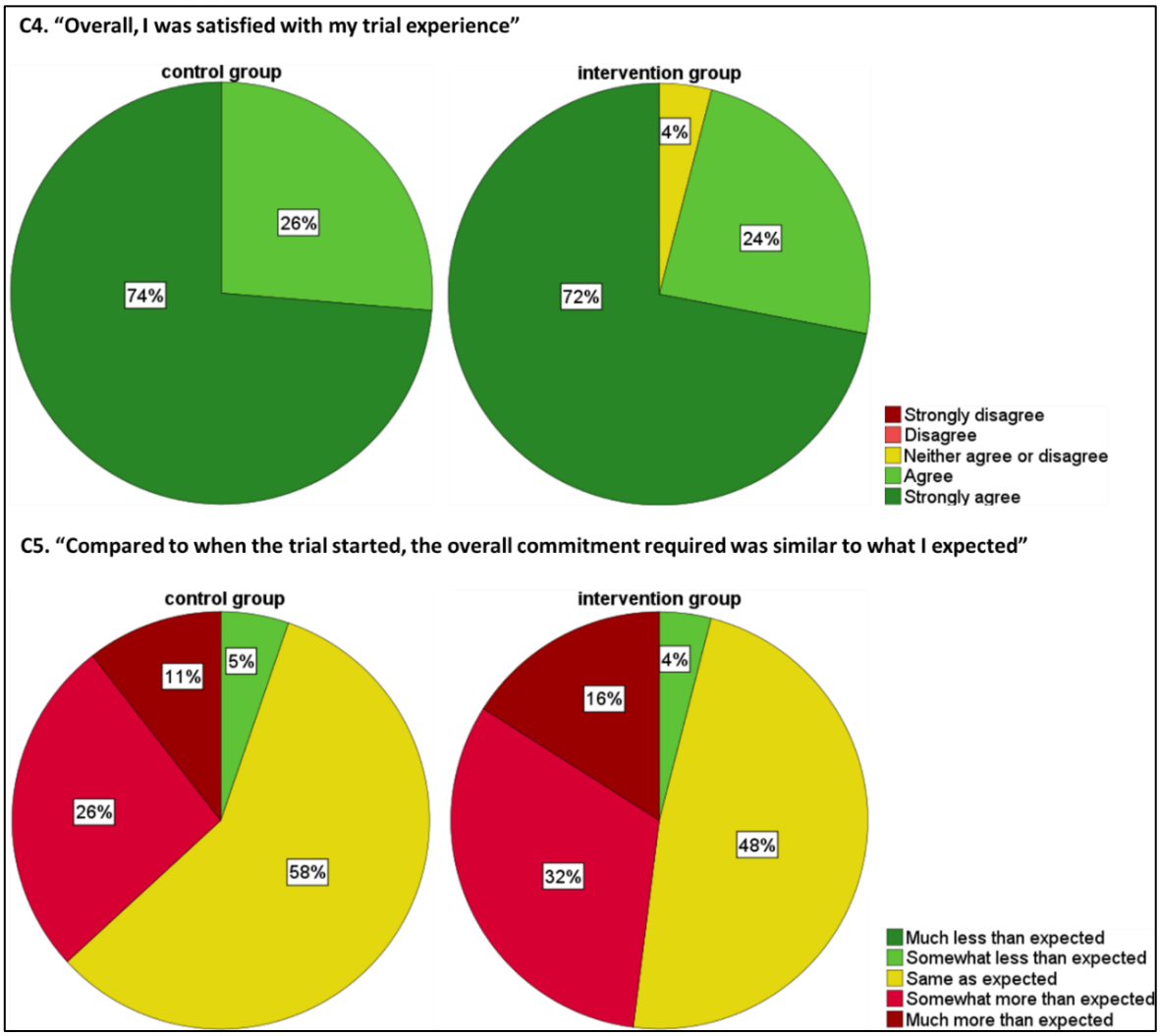


Figure 3: Study Participant Feedback Questionnaire (SPFQ): results for statement C4 and C5

Recruitment and attrition rates

The **recruitment** results are reported in detail in 5.1.

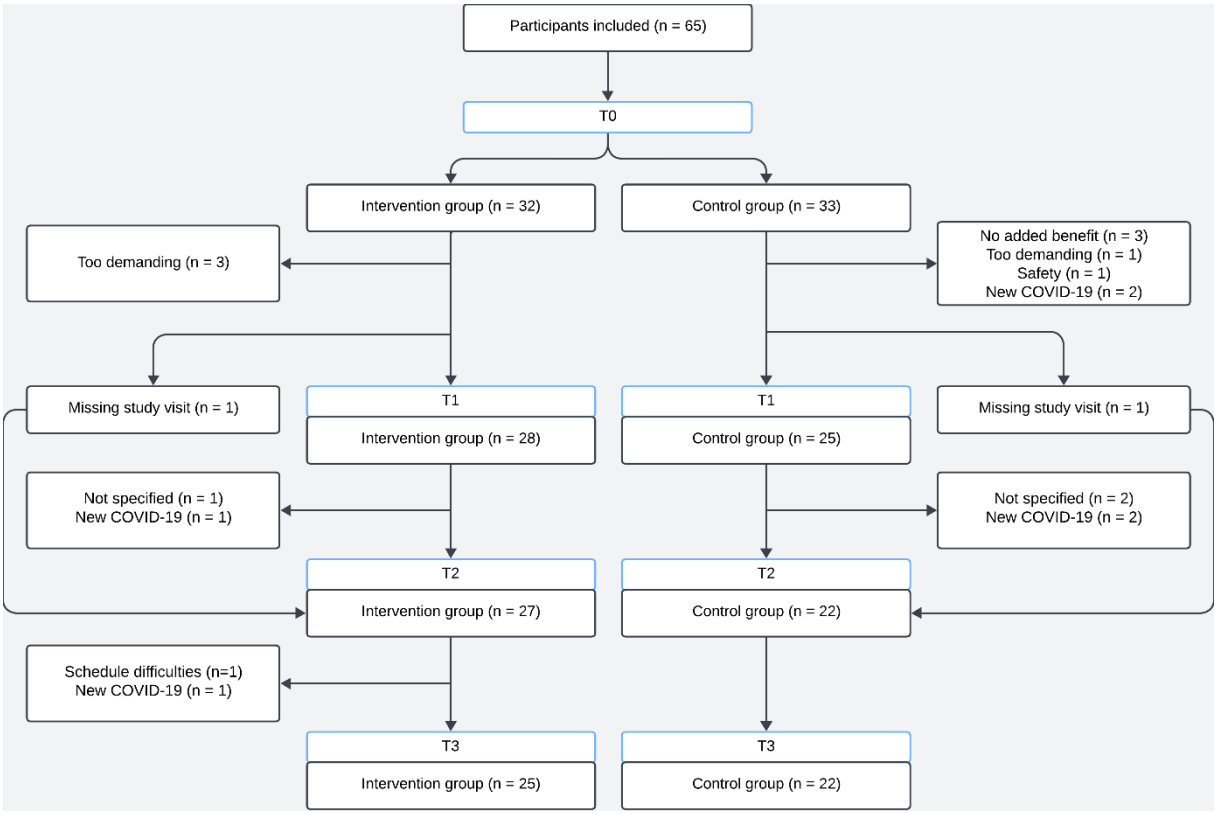
Out of the 65 participants that started the trial, 47 completed the trial. In **Error! Reference source not found.** the reasons for premature trial termination are shown. The most frequent reason was due to a new COVID-19 diagnosis (6 participants), followed by "study participation was physically too demanding" (4 participants). Interestingly, the 3 participants from the intervention group who gave this reason found the study visits the most demanding, compared to the single individual from the control group who found the physiotherapy sessions the most demanding.

Table 5: Reasons for premature trial termination

	Total (n = 18)	**Control group** (n = 11)	**Intervention group** (n = 7)
New COVID-19	6	4	2
Physically too demanding	4	1	3
No added benefit	3	3	0
Not specified	3	2	1
Too difficult to fit into schedule	1	0	1
Felt unsafe	1	1	0

To calculate the **attrition rate** we used the following formula: (number of participants with a missing T2)/(total number of participants) x 100. The reason for choosing the "number of participants with a missing T2" was that at T2 (12 weeks ± 7 days, end of intervention) the primary effectiveness outcome (1-MSTS) was assessed. Therefore, the attrition rate = 16/65 x100 = 24.6%, which is higher than the expected 20%. This will be taken into account in any future project proposals.

The following flowchart (Figure 4) shows the dropout of participants at each stage of the study.



T0: baseline; T1: 6 weeks ± 7 days; T2: 12 weeks ± 7 days (= end of intervention); T3: follow-up 6 weeks ± 7 days after end of intervention.

Figure 4: Participant attrition

Protocol adherence

To assess the feasibility of the trial, we also evaluated the protocol adherence. The most common deviation type was "missing procedures", including missing study visits, missing nutritional diaries and physical activity diaries, missing data of tests not performed during study visits, and missing weekly tele-consultations with the study dietitian. The second deviation type was "visit schedule".

Missing study visits

Two participants, one from each allocation group, missed T1. No data was collected for these participants at T1, however, they did attend the following study visits and interventions. The reasons for missing study visits were scheduling issues, therefore the missingness of the data is not related to the unobserved data, and we consider it Missing At Random, and consider it ignorable.

Missing data during the study visits

For the primary effectiveness outcome (1-Minute sit to stand test), there was one missing procedure at T0 and T1 because the participant's (different participant at each time point) long COVID symptoms (mostly fatigue) were too severe on the day of the study visit.

For one participant at T0, the indirect calorimetry could not be done due to unavailability of the disposable materials needed to perform the test. In the protocol, we provided a risk mitigation strategy, i.e. the use of the best fitting formula to calculate the resting energy expenditure.

Table 6 shows the sample size for the physical performance assessments that were used as explanatory outcomes. The yellow cells represent a lower sample size for analysis due to missing data. The main reasons were:

- Extreme fatigue (T1 all physical assessments: one participant; T2 all muscle strength assessments: one participant; T3 6-MWT: one participant)
- Pain (T0 left knee extension: one participant; T1 left elbow flexion: one participant, T1 right ankle dorsiflexion: one participant)
- Material malfunction (T2 all muscle strength assessments: one participant)
- eCRF malfunction (T0 right wrist extension: one participant)
- The occurrence of adverse events (T1 6-MWT: one participant, see on page 21).

Additionally, the muscle strength performed by some participants during the wrist extension was lower than the measuring threshold (12.1 N) at T0 (both sides: one participant, left side: one participant) and T1 (both sides: one participant).

Table 6: Sample size for the explanatory physical performance assessments

	T0			T1-T0			T2-T0			T3-T0		
	T	CG	IG	T	CG	IG	T	CG	IG	T	CG	IG
6-MWT	64	33	31	51	25	26	49	22	27	46	22	24
Muscle strength												
Shoulder (R)	64	33	31	52	25	27	47	21	26	47	22	25
Shoulder (L)	64	33	31	52	25	27	47	21	26	47	22	25
Elbow (R)	64	33	31	52	25	27	47	21	26	47	22	25
Elbow (L)	64	33	31	51	25	26	47	21	26	47	22	25
Wrist (R)	62	32	30	50	24	26	45	20	25	45	20	25
Wrist (L)	62	32	30	50	24	26	46	21	25	45	22	24
Hip (R)	64	33	31	52	25	27	47	21	26	47	22	25
Hip (L)	64	33	31	52	25	27	47	21	26	47	22	25
Knee (R)	64	33	31	52	25	27	47	21	26	47	22	25

Knee (L)	63	33	30	51	25	27	46	21	26	46	22	25
Ankle (R)	64	33	31	51	22	25	47	21	26	47	22	25
Ankle (L)	64	33	31	52	25	27	47	21	26	47	22	25
Handgrip strength	64	33	31	52	25	27	49	22	27	47	22	25

T: total sample, CG: control group, IG: intervention group, 6-MWT: 6-minute walk test, R: right side, L: left side; yellow cells: lower sample size not due to participant attrition.

Fatigue, pain, adverse events and low muscle strength all influence the value of the missing data; therefore, it is considered Missing Not At Random (MNAR). The data shows that the physical assessments are prone to be missing. This leads to a possible bias, as it can lead us to overestimate the results.

Missing nutritional and exercise diaries

Before each study visit, all participants were asked to complete a 3-day food diary. If the participant did not bring the completed diary to the study visit, they were reminded to complete it after and provide it via mail. The table below shows the amount of nutritional diaries missing per study visit, compared to the number of participants who completed that study visit. The amount of missing diaries was acceptable.

Table 7: Missing food diaries per study visit compared to the number of participants who completed the study visit.

Participants per study visit	Total # of missing diaries (%)
T0 (n = 65)	3 *(4.6%)*
T1 (n = 53)	5 *(9.4%)*
T2 (n = 49)	0 *(0.0%)*
T3 (n = 47)	2 *(4.2%)*

On the other hand, 39 out of the 65 participants did not complete the physical activity diary (60.0%). At the baseline study visit, the participants received a physical activity diary that they had to complete daily during the 12 weeks of intervention. They were asked to note the date, what kind of physiotherapy/exercise they performed, the intensity (0-10), duration (minutes), and if they experienced PESE/fatigue (Yes/No) after the activity. Of the submitted diaries, the majority is either incomplete (e.g., weeks missing) or incorrectly filled in. For example, some participants added any activity that caused fatigue and/or PESE such as reading, showering or social events. Some participants used the total duration instead of the actual duration of the physical activity (e.g., “vacuuming the bedroom” with a duration of 40 minutes, while in reality they may have vacuumed for 10 minutes with 30 minutes of rest in between vacuuming spurts).

During the study visits, the participants were asked to rank their physical activity level (PAL) as one of the following: inactive (<1.4) / sedentary (1.4) / moderately active (1.6)/ active (1.8) / very active (>1.8), in accordance with the Belgian High Health Council [30], with the intention to compare these answers to the physical activity reported in the diaries. The mean PAL was 1.6 ± 0.1 (i.e., moderately active) with a range between 1.3 and 2.0. After comparison with the physical activity in the diaries, we conclude that these answers are not accurate. Self-reported PAL and the used diaries to assess the

physical activity of individuals with long COVID is not feasible. We recommend the use of an objective assessment (e.g. ActiGraph accelerometer) in following studies.

Missing weekly teleconsultations

On average, participants in the intervention group had 10 ± 4 teleconsultation, with a minimum of 0 and a maximum of 13 consultations. Out of the 32 participants of the intervention group, 28 completed the intervention period (12 weeks). These participants had on average 11 ± 3 teleconsultations.

Adherence was calculated as the ratio of the number of teleconsultations that were carried out versus the number of planned consultations. Average adherence was 0.83 ± 0.28 for all intervention participants and 0.89 ± 0.22 for the intervention participants that reached the primary endpoint (T2). These results show a high feasibility for the weekly teleconsultations.

However, in the participants who had an early trial termination (n=4), the adherence was 0.45 ± 0.39. Two participants stopped because the trial (unspecified) was too demanding, one because the study visits were too demanding, and one participant had a new SARS-CoV-2 infection. Additionally, there were some participants with a particularly low adherence: one participant only had one out of twelve consultations, and one had four out of twelve. It is of special interest to include these participants in a future qualitative study to assess the facilitators and barriers for the nutritional intervention, as they can provide important information for its implementation.

Study visit schedule deviations

On average, study visits were planned within the timeline set by the protocol. The mean timeline was: T1 at 6 weeks, 1 day ± 3 days, T2 at 12 weeks, 2 days ± 4 days and T3 at 18 weeks, 3 days ± 6 days after the baseline study visit.

In total, 13 out of the 214 study visits (6%) were performed outside of the set timeline. Three T1 study visits (3 CG) were performed on average 4 days later, five T2 five study visits (3 IG, 2 CG) were planned on average 2 days too late, and six T3 study visits (2 IG, 4 CG) were planned on average 5 days too late. The main reason for this delay was that some participants and/or the assessor had to reschedule the planned appointment due to unforeseen circumstances like illness, familial or work emergencies. The study visit schedule deviations were therefore considered acceptable.

5.4.2. Effectiveness outcome

The following table (Table 8) shows the baseline results for the 1-minute sit to stand (1-MSTS) test. In general, participants in the control group performed 24 ± 10 repetitions and participants in the intervention group performed 24 ± 6 repetitions. Based on reference values in healthy adults [33], **the mean results at baseline were low** (around the 2.5th percentile). There are no reference values for the 1-MSTS in individuals with long COVID, although one study in COVID-19 survivors 3-11 months after hospital discharge found a mean of 19 ± 6 repetitions [34].

The Minimal Clinically Important Difference (MCID) is +3 repetitions, based on the validation of the 1-MSTS in COPD patients [35]. Table 9 shows the difference in repetitions between each study visit and the baseline measurement. At the primary effectiveness outcome of this pilot, i.e. at T2, **the mean difference in 1-MSTS repetitions was 3 [95% CI: 0, 5] repetitions in the control group, and 4 [95% CI: 2, 5] in the intervention group. The mean difference between the intervention group and the control**

group was 1 [95% CI: -2, 4]. Although there was no statistically significant mean difference between the intervention and the control group (mean difference: 1 [95% CI: -2, 3]), the within group difference throughout the trial increased in both groups, indicating a clinical improvement. This improvement continued after T2, with a difference of 3 [95% CI: 1, 6] in the control group and 5 [95% CI: 3, 8] in the control group at T3. Additionally, the estimated effect between the groups increased over the trial duration, from a mean difference of 1 [95% CI: -2,3] at T1 to a mean difference of 2 [95% CI: -1, 6] at T3. Figure 5: Difference in 1-minute sit-to-stand test (1-MSTS) repetitions between each study visit and baseline shows the difference in 1-MSTS repetitions between each study visit and baseline.

Table 8: descriptive baseline results of the 1-MSTS

	Total (mean ± SD)	**CG (mean ± SD)**	**IG (mean ± SD)**
	n = 64	*n = 33*	*n = 31*
T0 repetitions	24 ± 8	24 ± 10	24 ± 6

Table 9: descriptive results of the 1-MSTS throughout the trial

	Total ***mean [95%CI]***	**CG** ***mean [95%CI]***	**IG** ***mean [95%CI]***	**Mean difference between IG and CG** ***mean [95%CI]***
	n = 52	*n = 25*	*n = 27*	
Difference in repetitions T1-T0	2 [1, 3]	2 [0, 4]	2 [1, 4]	1 [-2, 3]
	n = 49	*n = 22*	*n = 27*	
Difference in repetitions T2-T0	3 [2, 4]	3 [0, 5]	4 [2, 5]	1 [-2, 4]
	n = 47	*n = 22*	*n = 25*	
Difference in repetitions T3-T0	4 [3, 6]	3 [1, 6]	5 [3, 8]	2 [-1, 6]

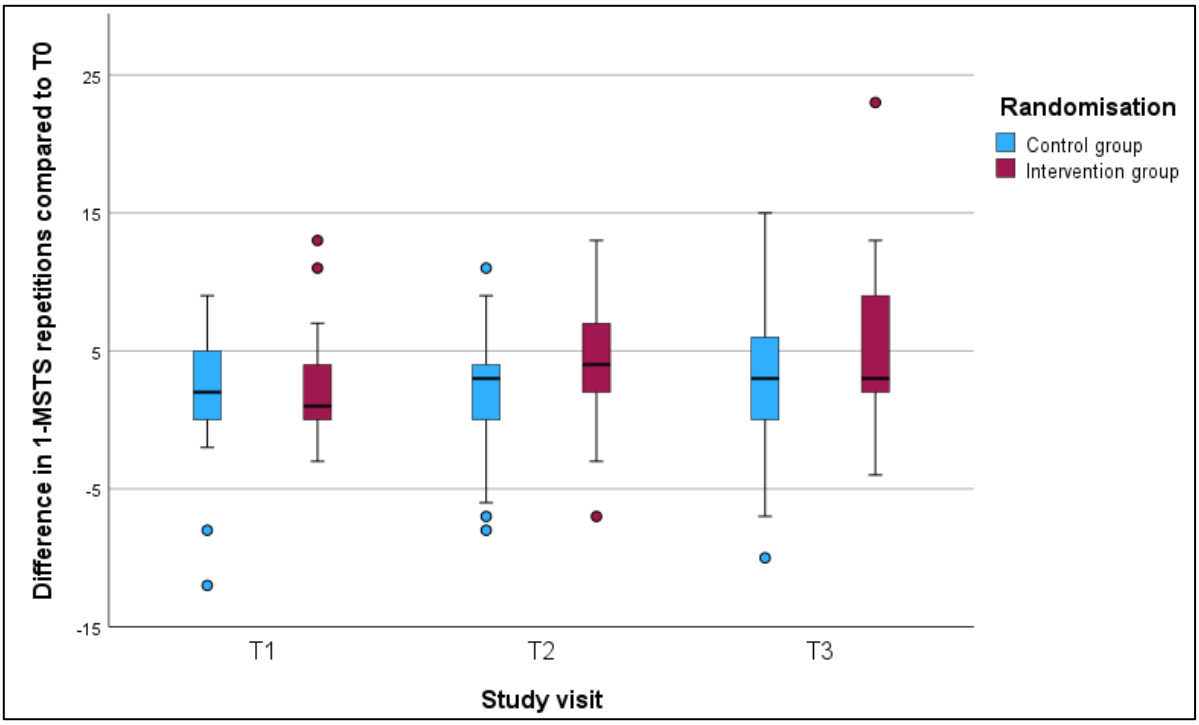


Figure 5: Difference in 1-minute sit-to-stand test (1-MSTS) repetitions between each study visit and baseline (T0)

T1: 6 weeks ± 7 days, T2: 12 weeks ± 7 days (end of intervention), T3: 18 weeks ± 7 days (6 weeks follow-up). The boxplots are shows for both groups. The boxes show the median and inter-quartile ranges. The whiskers show the minimum and maximum values. The dots present the outliers.

Based on these data, we can calculate the sample size that would be necessary to show a statistically important difference in functional performance recovery (i.e., difference in 1-MSTS repetitions) between both, using G*Power software (Düsseldorf, Germany). Based on the effect size we found in this pilot study for the 1-MSTS between experimental and control group (effect size: d = 0.212, α = 0.05, power = 0.80, test family: F-tests, statistical test: ANOVA, repeated measures, between factors, type of power analysis: a priori). Considering a 24.6% loss to follow-up in participants (see 5.4.1), a sample size of 142 individuals with long COVID needs to be recruited.

6. CONCLUSION

6.1. Feasibility of the UNLOCK trial

The primary objective of this pilot study was to assess the **feasibility** of the personalized multimodal treatment (PMT), consisting of individualized physiotherapy in combination with personalised nutritional counselling, in the long COVID population, as well as the feasibility of the study design. The focus was participant **study burden, recruitment and attrition rates, and protocol deviations**.

We assessed study burden during the feedback consultation using the Study Participant Feedback Questionnaire (SPFQ) version 1.0 - section C (n = 44). In the control group, 26% agreed and 74% strongly agreed to be satisfied with their trial experience, similar to the participants of the intervention group, of which 24% agreed and 72% strongly agreed to be satisfied. In contrast, the majority found the required commitment similar (58% in the control group, 48% in the intervention group), somewhat more (26% in the control group, 32% in the intervention group), or much more (11% in the control group, 16% in the intervention group) than expected. Based on these results, we conclude although the study burden was high, participants were satisfied with their experience, indicating that the **study burden was acceptable.** However, these results are possibly biased, as 32.3% of all participants, and none of the participants who withdrew from the trial completed the SPFQ. Additionally, **expected study burden was an important limiting factor in the recruitment for this study**, as 18 individuals of the 60 who failed the pre-screening (30%), indicated not to be interested in participating in the trial due to distance or expected time commitment.

Despite a great number of individuals living with long COVID, and a variety of recruitment strategies, **recruitment was slower than expected (16 months instead of the anticipated 10 months**). The most successful recruitment strategies were referral by other medical doctors within the study site (38 individuals or 26%) and mentions of the trial in the media by the Principal Investigator (29 individuals or 20%). In total, 146 individuals contacted the study site, 141 received a pre-screening of which 81 (57%) passed, 73 individuals received a medical screening and finally **65 individuals consented to participation to the trial**. This was lower than the predefined goal of 66 participants, due to time restraints. Of these participants, 47 completed the trial. The most frequent reason for premature trial termination was due to a new COVID-19 diagnosis (n = 6), followed by “study participation was physically too demanding” (n = 4). The calculated **attrition rate** (based on the number of participants with a missing primary effectiveness outcome) **was 24.6%, which is higher than the expected 20%.**

The last way to assess the feasibility of the trial was to evaluate the protocol adherence. The most common deviation type was “missing procedures”. This included missing study visits (n = 2), missing data during the study visits, missing diaries and missing weekly tele-consultations with the study dietitian. Importantly, the **missing data during the study visits primarily included physical assessments that were not performed due to extreme fatigue or pain**, among other reasons. This leads to a possible bias, as it can lead us to overestimate the results. The amount of **missing nutritional diaries was acceptable** (4.6% at T0, 9.4% at T1, 0% at T2 and 4.2% at T3). On the other hand, **39 out of the 65 participants did not complete the physical activity diary (60.0%)**. A possible explanation is that the burden on the participant to complete this diary throughout the 12 weeks was too high. We recorded additional information on the physiotherapy in 27 participants (11 from the control group and 16 from the intervention group. These **participants reported that they used 14 (25th-75th percentile: 12-18) out of the 18 prescribed sessions within the 12 weeks of intervention**. The amount

of sessions was slightly higher in the intervention group (15 vs. 12 sessions in the control group). The weekly **teleconsultations with the study dietitians showed a high feasibility**, with an average **adherence of 0.83 ± 0.28** for all intervention participants, with a **mean of 10 ± 4 teleconsultations in the 12 weeks** of intervention. However, in the participants who had an early trial termination (n=4), the adherence was 0.45 ± 0.39, and there were some participants with a particularly low adherence: one participant only had one out of twelve consultations, and one had four out of twelve. A second deviation type was "study visit schedule", however, these deviations were less common (6% of visits) and we can conclude that overall the study visits were planned within the timeline set by the protocol.

To summarise, the predetermined conditions regarding the participant recruitment and attrition were not met: recruitment took 16 months instead of 10 months, 65 participants instead of 66 were recruited and attrition rate was 24.6% compared to the anticipated 20%. Based on the data gathered in this study, the (expected) study burden was an important limiting factor in both recruitment and attrition. On the other hand, participants who completed the trial (44 participants or 67.7%) indicated that although the study burden was high, they were satisfied with their trial experience. Additionally, the data from this pilot study shows that the intervention-specific procedures were highly feasible: both the nutritional counselling and the physiotherapy sessions show a high adherence, with a mean of 10 ± 4 teleconsultations with the study dietitians and 15 physiotherapy sessions in 12 weeks. The majority of protocol deviations happened during the study visits, mostly due to long COVID-specific symptoms such as fatigue or pain.

6.2. Effectiveness of the PMT

To assess the **effectiveness** of this PMT, we evaluated if the PMT can improve the functional performance recovery in individuals with long COVID faster compared to standard physiotherapy alone, using the 1-minute sit to stand test (1-MSTS).

As expected, and based on reference values in healthy adults, **the mean results at baseline were low** in both groups. On average, **participants performed 24 ± 8 repetitions** (24 ± 10 in the control group, 24 ± 6 in the intervention group). At T2, **the mean difference in 1-MSTS repetitions the mean difference in 1-MSTS repetitions was 3 [95% CI: 0, 5] repetitions in the control group, and 4 [95% CI: 2, 5] in the intervention group. The mean difference between the intervention group and the control group was 1 [95% CI: -2, 4].**

To show a statistically and clinically important difference in functional performance recovery (i.e., difference in 1-MSTS repetitions), we calculated a sample size of 142 individuals with long COVID for e large-scale RCT that assesses the effectiveness of the PMT.

7. DISCUSSION

The UNLOCK study is a randomized controlled interventional pilot study designed to gain insight into new treatment options for people affected by long COVID. The intervention was developed to improve functional performance. As a pilot study, the UNLOCK study is not powered to show treatment efficacy. However, it does provide some first insights in the feasibility of the study protocol. Secondly, this pilot study gives us an idea about whether the intervention would improve certain symptoms of people with long COVID.

A total of 65 participants enrolled in this study, with a mean age was of 43 ± 10 years, 64.6% being female, and a mean BMI of 25.8 ± 4.1 kg/m². The majority of participants had a mild COVID-19 infection, 9.2% was hospitalised during the acute infection, with an average hospitalisation length of 16 ± 18 days (range: 3 – 46 days). Based on the literature, the current sample fits the expected profile of the long COVID population [36, 37]. For this pilot, the study team aimed for 52 participants in line with Whitehead et al. recommending a sample size of 25 per treatment arm of interest in a pilot study, accounting for a standardised mean difference of 0.2 in the future definitive RCT with a power of 90%, and two-sided 5% significance (46). Considering an attrition rate of 20%, 66 participants will be randomised. Based on the results of this study regarding effect size of the primary outcome, physical performance measured using the 1 MSTS (d = 0.212) and attrition rate in this long COVID population (24.6%), resulting in a sample of 142 participants.

For the primary effectiveness outcome of this pilot study (T2), the mean difference in 1-MSTS repetitions was 3 [95% CI: 0, 5] within the control group, 4 [95% CI: 2, 5] within the intervention group, and 1 [95% CI: -2, 4] between the intervention group and the control group. The clinical improvements continued through T3. Looking at the MCID (being +3 repetitions based on COPD patients), both groups made clinical improvement, however, the increasing (although insignificant) effect between groups can be attributed to the greater and faster improvement within the intervention group compared to the control group. The trend of the differences between the control and intervention groups increasing over time suggests that the follow-up period of this pilot study may not have been sufficiently long. Pilot studies often have shorter durations to quickly evaluate feasibility and preliminary efficacy. The duration of the intervention might have been too brief to reveal significant changes in long COVID symptoms, although clinically relevant differences were observed.

Furthermore, there are some methodological aspects that may have influenced possible differences between the control and intervention groups in this pilot trail. A first of which is “measurement sensitivity”. Measurement sensitivity refers to the ability of an instrument or method to detect changes or differences when they occur. In the context of long COVID, where symptoms can be highly variable and multifaceted, it is crucial to use measurement tools that are sensitive enough to capture subtle improvements or deteriorations in a patient’s condition. Considering that long COVID is also a fairly new condition, hardly any of the measurement tools used have been validated in this population. This could result in an underestimation of the true effects of the intervention. Utilizing precise and long COVID-validated measures might be necessary to accurately assess the impact of this intervention on long COVID patients.

Also, long COVID is characterized by a wide range of symptoms that can affect multiple body systems, including respiratory, cardiovascular, neurological, and gastrointestinal systems, among others. The heterogeneity in symptom presentation might imply that patients have diverse needs and responses to interventions. Also, these symptoms can fluctuate unpredictably over time. This variability can obscure the benefits of the interventions, as improvements might be temporary or overshadowed by new or recurring symptoms. Cognitive difficulties, such as brain fog, can hinder patients' ability to follow nutritional advice, reducing the potential benefits of the intervention. In addition, participants reported that completing the many questionnaires prior to the study visit was perceived as tiring, which in turn may have led to PESE on the day of the measurements.

Overall, this pilot study was found feasible. Methodological factors, but also the variability in symptoms create a highly individualized recovery process. Future studies may need to consider stratified or personalized approaches that account for these variables, potentially enhancing the effectiveness of interventions by addressing the unique needs of each patient. To draw more definitive conclusions, further research with larger sample sizes, longer follow-up periods, and potentially different designs or intervention components might be necessary. Such a study should address the limitations of the pilot study and incorporate comprehensive methodologies to ensure robust and generalizable results. Such a study will provide definitive evidence on the efficacy and cost-effectiveness of the intervention, guiding clinical practice and healthcare policy to better support long COVID patients. Additionally, qualitative research could help understand patient experiences and adherence issues that quantitative measures might miss.

8. GO/NO-GO CRITERIA FOR MOVING TO A FULL TRIAL

Table 10 shows the predetermined criteria that need to be met before moving to a large-scale RCT. The criteria were met for consent rate and risk. The criteria were not met for recruitment rate, eligibility, screen failure, recruitment or attrition. However, we believe that by reducing the study burden, which is an important contributor to both the recruitment and attrition outcomes, these results can be mitigated.

Table 10: Targets and results of the Go/No-Go criteria

	Anticipated	**Actual**
Recruitment rate	100 individuals screened in 10 months (average 10/month)	141 individuals screened in 16 months (average 9/month)
Eligibility	90%	57%
Consent rate	80%	80%
Screen failure	10%	43%
Recruitment	66 participants	65 participants
Attrition	< 20%	24.6%
Risk	Comparable to standard of care	Comparable to standard of care

9. PROPOSAL FOR THE DEVELOPMENT OF A FULL TRIAL

This pilot provided valuable insights and underscores the necessity of conducting a larger, powered study to definitively assess the efficacy of a multimodal approach. This full powered RCT should address the limitations of the pilot study and incorporate comprehensive methodologies to ensure robust and generalizable result:

To enhance the geographical and demographic diversity, and to improve recruitment and reduce attrition, it is important to include more study centres throughout Belgium in any future projects. These centers can provide a representative sample of the population, ensuring that the study results are applicable across different regions and healthcare settings. This would also reduce travel time and distance for the participants, lowering the expected time commitment.

It is also important to account for the higher attrition rate. Reducing the number of outcomes and/or number of study visits would significantly reduce the study burden, allowing for a better retention of participants and less missing data during the study visits. We concluded that the study burden was acceptable. However, only 32.3% of all participants, and none of the participants who withdrew from the trial, completed the Study Participant Feedback Questionnaire. As a result, no feedback is available from this group of participants in terms of the feasibility of the study. Additionally, participants who withdrew from the study had a lower adherence to the intervention-specific procedures.

A clear and detailed statistical plan is essential for the success of the powered study. This plan should include: an adjusted sample size calculation: based on the effect sizes observed in the pilot study, the sample size should be calculated to ensure adequate power to detect clinically meaningful differences between groups; robust randomization procedures and blinding protocols should be implemented to minimize bias and ensure the integrity of the study results. Last, the statistical plan should include data analysis methods: advanced statistical techniques should be outlined, including methods for handling missing data, subgroup analyses, and adjustments for potential confounders.

Involving a healthcare utilization group will provide critical insights into the economic and resource implications of the multimodal intervention. This group will evaluate the utilization of healthcare resources by patients in both the intervention and control groups, conduct cost-effectiveness analyses to determine the financial viability and potential savings associated with the multimodal intervention, and develop recommendations for healthcare policy based on the findings, potentially influencing the adoption of effective interventions for long COVID in healthcare systems.

Another aspect we would focus on with this study is clearly outlining patient pathways and ensuring their involvement in the study design and implementation will enhance the relevance and acceptability of the research. This involves detailed mapping of patient pathways from recruitment to follow-up, ensuring that all steps are transparent and patient-centric, engaging patients in the design phase to incorporate their perspectives and preferences, ensuring that the intervention is tailored to their needs. Maintaining regular communication with patients throughout the study, providing updates, and collecting feedback to improve the study process and outcomes is of great importance.

Finally, it is important to note that certain socio-economic and socio-demographic factors may also play an influence. For instance, we know from at least 1 participant in the intervention group that she did not have the financial means nor the social support to follow the dietician's advice. These data were not questioned during this pilot, yet would be of great value when conducting a full-powered RCT.

10. Additional observations

The first aim of the UNLOCK study was to assess the feasibility of the study design and of the PMT in the long COVID population, and to assess the effectiveness of this PMT before conducting a large scaled RCT. The second aim was to get a **better understanding of the data**, because of the heterogeneity of the long COVID population. The UNLOCK study protocol included additional secondary and explanatory outcomes. These will be described in the following sections. **As a pilot study, the UNLOCK study is not powered to show effects in any of the following outcomes, however, exploring these outcomes can show promising results that should be considered when designing future projects**. As such, **several outcomes were found to have 95% confidence intervals that did not include zero, suggesting statistically significant differences, despite the limited sample size.** These findings warrant further investigation in larger, adequately powered studies to confirm these effects. The analyses that were performed in the following sections are illustrative.

10.1. Secondary outcomes

In **Error! Reference source not found.**Table 11 the results for the secondary outcomes at baseline are shown as the median and 25th – 75th percentiles. Table 12 shows the mean difference (95% Confidence Interval) in the outcomes between each study visit and baseline.

10.1.1. Fatigue

To assess the change in fatigue throughout the participation in the study, we used the Multi-dimensional Fatigue Inventory (MFI-20). It consists of five subscales: general fatigue, physical fatigue, reduced activities, reduced motivation, and mental fatigue. The score for each of the subscales can range from minimally 4 to maximally 20. The MFI-scores in our study population were right-skewed, indicating **high fatigue, with a median of 18 for general and physical fatigue, 15 for reduced activities and mental fatigue, and 12 for reduced motivation**. Neither the control group nor the intervention group show a significant improvement at 12 weeks ± 7 days (T2), based on the MCID of approximately -2 for each subscale [38]. However, we can see a **near-significant positive trend for the intervention group** but not for the control group **at 18 weeks ± 7 days** (T3), for **general fatigue** (-1.28 [95% CI: -2.59, 0.03]), **reduced activities** (-1.48 [95% CI: -2.96, 0.00]), **and mental fatigue** (-1.44 [95% CI: -2.93, 0.05]). As 77% of participants reported to continue with the intervention after T2 (see further), **this result shows promise for a longer interventional period in future studies**.

10.1.2. Health-related quality of life

To assess the health-related quality of life, we used the EuroQol Group 5 dimensions 5 levels (EQ-5D-5L) questionnaire. This questionnaire comprises of 5 dimensions: mobility, self-care, usual activities, pain, and anxiety. Each has 5 levels from no problems (score 0) to extreme problems/inability (score 4). At baseline, the study population showed **severe issues** (median score 3) **with usual activities** (25th-75th percentile: 3-4) **and pain** (25th-75th percentile: 2-4), **moderate issues** (median score 2) **with mobility** (25th-75th percentile: 1-3) **and anxiety** (25th-75th percentile: 1-3), **and slight issues with self-care** (median score 1, 25th-75th percentile: 1-2). A study in individuals with long COVID found the MCID for the EQ-5D levels, namely a change of at least 0.262 [39]. In general, **all dimensions showed clinical improvement throughout the trial participation**, **especially in the control group**. In the control group, we saw significant changes at T2 compared to baseline for mobility (-0.75 [95% CI: -1.09; -0.41]), usual activities (-1.10 [95% CI: -1.50; -0.70], pain (-0.50 [95% CI: -1.18; -0.22]) and anxiety ((-0.50 [95% CI: -0.89; -0.11]). In the intervention group we saw significant changes at T2 compared to baseline for usual

activities (-0.48 [95% CI: -0.75; -0.21]), and anxiety (-0.48 [95% CI: -0.88; -0.08]). At T3, a significant clinical difference was seen for all levels in the control group and in usual activities, pain and anxiety for the intervention group, suggesting that the PMT as designed in this pilot study might be too demanding when it comes to quality of life, and that a longer, yet less demanding, interventional period might be promising.

Additionally, the EQ-5D-5L contains a self-rated health status on a vertical visual analogue scale (VAS) where the endpoints are labelled '*the best health you can imagine*' (100) and '*the worst health you can imagine*' (0**). At baseline, the study population reported a self-rated health status of 50. This also showed improvement throughout the trial participation, based on the MCID of 7.5** [39]**, mostly in participants in the control group**. At T2 the control group scored 14.10 more (95% CI: 6.19, 22.01) compared to 7.72 (95% CI: 0.45, 14.99) in the intervention group. The positive evolution continued through T3, with 16.30 (95% CI: 9.92, 22.68) points higher in the control group versus the 7.24 (95% CI: -0.28, 14.76) in the intervention group.

While both groups show a positive trend, we do not have sufficient information to interpret the differences between the groups.

10.1.3. Functional Status

The Post-COVID-19 Functional Status (PCFS) scale was specifically designed to assess the functional status in individuals recovering from a SARS-CoV-2 infection. The overall PCFS scale grade corresponds with the poorest functional status indicated by the participant's answers. **The median PCFS scale grade was 3 (25th-75th percentile: 2-3) at baseline** (see Table 12), indicating **"moderate functional limitations",** although they did not have any functional limitations before COVID-19. This means that the participants had to modify or avoid usual activities at home and/or at work due to symptoms. This self-reported functional status showed a **slight positive trend with a change of - 0.40 [95% CI: -0.75; -0.05] for the control group compared to -0.12 [95% CI: -0.37; 0.13] in the intervention group at T2.** Although this shows some improvement, it cannot be considered clinically important.

One similar study compared the PCFS scale in 39 participants either receiving a supervised exercise program (intervention) or following a self-management leaflet based on the WHO guidelines for long COVID rehabilitation for 8 weeks [40]. Both groups had a baseline PCFS grade similar to the one in our study population (control group: 2.5 ± 1.0, intervention group: 2.6 ± 1.1). Post-test, the PCFS scale in the intervention group was 1.1 ± 1.2, compared to 1.8 ±1.1 in the control group, which was considered significant (p = 0.033).

10.1.4. Work-related activities

With the Work Productivity and Activity Impairment (WPAI) questionnaire, the work-related activities were evaluated. At baseline, 69.2% of participants (72.7% in the control group and 65.6% in the intervention group) reported to have paid employment, which does correspond with the Belgian average of 72.1% of 20–64-year-olds in 2023 [41]. It is interesting to note that this number is higher than the 46.0 % of participants (46.4% in the control group and 45.5% of participants in the intervention group) that reported not to be on sickness leave at baseline. The best explanation for this difference is that an "employed person" can be temporarily absent for illness (i.e., on sickness leave) or other reasons, while still being considered employed.

The employed participants (n = 45) reported that on median, they missed 18 workhours (25^{th}-75^{th} percentile: 0 – 37) due to health problems. This was higher in the control group with 20 hours (25^{th}-75^{th} percentile: 0 – 38) compared to the intervention group with 5 hours (25^{th}-75^{th} percentile: 0 - 31). The workhours worked were similar, with the control group working on median 13 hours (25^{th}-75^{th} percentile: 0 – 23) and the intervention group 14 hours (25^{th}-75^{th} percentile: 4 - 26). In addition, the level at which the health problems affect their productivity while working was also similar in both groups, with both groups giving a self-reported median score of 6 out of 10 (control group 25^{th}-75^{th} percentile: 3 - 7, intervention group 25^{th}-75^{th} percentile: 5 - 8). All participants, including those without paid employment (n = 65), were asked how much the health problems affect their ability to perform normal activities. At baseline, the control group reported a score of 5 out of 10 (25^{th}-75^{th} percentile: 3 - 7) and the intervention group a score of 7 out of 10 (25^{th}-75^{th} percentile: 5 - 8).

The WPAI questionnaire results did not show any significant changes throughout the duration of the study, except for the work hours worked at T2, with the intervention group working a mean of +9.01 hours [95% CI: 2.24; 15.78] compared to baseline. This significant change was not continued after T2.

10.1.5. Health-related mental health

Mental status was evaluated using the Hospital Anxiety and Depression Scale (HADS) during each study visit. This test is a simple tool to assess both anxiety and depression, each with 7 questions indicating a low (0) to high (3) score for anxiety and/or depression. A subscale score of less than seven indicates non-cases, 8-10 indicates a mild case, 11-14 moderate case and 15-21 a severe case of anxiety and/or depression [42]. The median score at baseline for our study population was 8 (25^{th}-75^{th} percentile: 6-10) for depression, and 9 (25^{th}-75^{th} percentile: 6-14) for anxiety. This shows that **the majority of the study population suffered from at least mild to moderate depression and anxiety at baseline**. There were **no significant changes throughout the duration of the study.**

Table 11: Descriptive results for the secondary outcomes at baseline

	Total n = 65	**CG n = 33**	**IG n = 32**
Fatigue			
General fatigue (median, Q1 - Q3)	18 (15 - 20)	17 (15 - 19)	19 (15 - 20)
Physical fatigue (median, Q1 - Q3)	18 (15 - 19)	17 (15 - 19)	18 (16 - 19)
Reduced activities (median, Q1 - Q3)	15 (14 - 18)	15 (13 - 17)	17 (14 - 18)
Reduced motivation(median, Q1 - Q3)	12 (10 - 15)	12 (10 - 15)	12 (10 - 14)
Mental fatigue (median, Q1 - Q3)	15 (11 - 18)	16 (10 - 18)	15 (11 - 18)
Health-related quality of life			
Mobility (median, Q1 - Q3)	2 (1 - 3)	2 (1 - 3)	2 (1 - 3)
Self care (median, Q1 - Q3)	1 (1 - 2)	1 (1 - 2)	1 (1 - 2)
Usual activities (median, Q1 - Q3)	3 (3 - 4)	3 (3 - 4)	3 (3 - 4)
Pain (median, Q1 - Q3)	3 (2 - 4)	3 (2 - 4)	3 (2 - 4)
Anxiety (median, Q1 - Q3)	2 (1 - 3)	2 (1 - 3)	2 (2 - 3)
VAS (median, Q1 - Q3)	50 (36 - 60)	50 (40 - 60)	50 (60 - 65)
Functional status			
PCFS scale grade (median, Q1 - Q3)	3 (2 - 3)	3 (2 - 3)	3 (2 - 3)
PCFS flow before COVID-19 (median, Q1 - Q3)	0 (0)	0 (0)	0 (0)
Work-related activities			
Paid employment (% yes)	69.2	72.7	65.6
Work-hours missed due to health problems (median, Q1 - Q3)	18 (0 - 37)	20 (0 - 38)	5 (0 - 31)
Work-hours missed due to other reasons (median, Q1 - Q3)	0 (0 - 7)	0 (0 - 4)	1 (0 - 11)
Work-hours worked (median, Q1 - Q3)	14 (0 - 25)	13 (0 - 23)	14 (4 - 26)
How much did your health problems affect your productivity while you were working (0-10) (median, Q1 - Q3)	5 (3 - 7)	6 (3 - 7)	6 (5 - 8)
How much did your health problems affect your ability to perform normal activities (0-10) (median, Q1 - Q3)	7 (5 - 8)	5 (3 - 7)	7 (5 - 8)
Health-related mental health			
Depression (median, Q1 - Q3)	8 (6 - 10)	9 (6 - 10)	8 (6 - 10)
Anxiety (median, Q1 - Q3)	9 (6 - 14)	9 (7 - 14)	10 (6 - 14)

Table 12: Difference in secondary outcomes between each study visit and baseline

	T1-T0			T2-T0			T3-T0		
	Total n = 45	CG n = 20	IG n = 25	Total n = 45	CG n = 20	IG n = 25	Total n = 45	CG n = 20	IG n = 25
Fatigue									
General fatigue (mean, 95% CI)	.16 [-.86, 1.17]	-.45 [-2.14, 1.24]	.64 [-.68, 1.96]	-.20 [-1.36, .96]	-.10 [-2.31, 2.11]	-.28 [-1.55, .99]	-.71 [-2.09, .67]	.00 [-2.79, 2.79]	-1.28 [-2.59, .03]
Physical fatigue (mean, 95% CI)	-.27 [-1.25, .72]	-.55 [-2.04, .94]	-.04 [-1.44, 1.36]	-.38 [-1.27, .52]	-.10 [-1.59, 1.39]	-.60 [-1.78, .58]	-1.22 [-2.35, -.10]	-.10 [-1.44, 1.24]	-2.12 [-3.84, -.40]
Reduced activities (mean, 95% CI)	.29 [-.66, 1.23]	.80 [-.72, 2.32]	-.12 [-1.38, 1.14]	-.36 [-1.29, .58]	-.30 [-1.56, .96]	-.40 [-1.83, 1.03]	-1.11 [-2.08, -.15]	-.65 [-1.90, .60]	-1.48 [-2.96, .00]
Reduced motivation (mean, 95% CI)	.40 [-.82, 1.62]	.45 [-1.96, 2.86]	.36 [-.89, 1.61]	-.42 [-1.59, .75]	-.25 [-2.38, 1.88]	-.56 [-1.96, .84]	-.49 [-1.60, .62]	-.15 [-2.21, 1.91]	-.76 [-2.03, .51]
Mental fatigue (mean, 95% CI)	-.20 [-1.13, .73]	-.20 [-1.98, 1.58]	-.20 [-1.23, .83]	-.24 [-1.34, .85]	-.30 [-2.49, 1.89]	-.20 [-1.31, .91]	-.89 [-2.07, .29]	-.20 [-2.20, 1.80]	-1.44 [-2.93, .05]
Health-related quality of life									
Mobility (mean, 95% CI)	-.20 [-.49, .09]	-.50 [-.89, -.11]	.04 [-.38, .46]	-.42 [-.67, -.18]	-.75 [-1.09, -.41]	-.16 [-.49, .17]	-.33 [-.56, -.11]	-.60 [-.95, -.25]	-.12 [-.39, .15]
Self care (mean, 95% CI)	-.07 [-.20, .07]	-.10 [-.31, .11]	-.04 [-.23, .15]	-.13 [-.27, .00]	-.20 [-.44, .04]	-.08 [-.25, .09]	-.11 [-.27, .05]	-.25 [-.46, -.04]	.00 [-.24, .24]
Usual activities (mean, 95% CI)	-.53 [-.81, -.26]	-1.05 [-1.37, -.73]	-.12 [-.48, .24]	-.76 [-1.00, -.51]	-1.10 [-1.50, -.70]	-.48 [-.75, -.21]	-.82 [-1.08, -.56]	-1.20 [-1.56, -.84]	-.52 [-.86, -.18]
Pain (mean, 95% CI)	-.42 [-.70, -.15]	-.60 [-.92, -.28]	-.28 [-.72, .16]	-.51 [-.80, -.22]	-.70 [-1.18, -.22]	-.36 [-.73, .01]	-.51 [-.72, -.30]	-.55 [-.87, -.23]	-.48 [-.77, -.19]
Anxiety (mean, 95% CI)	-.47 [-.71, -.22]	-.50 [-.86, -.14]	-.44 [-.80, -.08]	-.49 [-.76, -.22]	-.50 [-.89, -.11]	-.48 [-.88, -.08]	-.42 [-.64, -.21]	-.40 [-.75, -.05]	-.44 [-.73, -.15]
VAS (mean, 95% CI)	6.64 [1.75, 11.53]	9.85 [1.93, 17.77]	4.08 [-2.36, 1.52]	1.56 [5.33, 15.78]	14.10 [6.19, 22.01]	7.72 [.45, 14.99]	11.27 [6.22, 16.31]	16.30 [9.92, 22.68]	7.24 [-.28, 14.76]
Functional status									
PCFS scale grade (mean, 95% CI)	.00 [-.19, .19]	.00 [-.34, .34]	.00 [-.24, .24]	-.24 [-.45, -.04]	-.40 [-.75, -.05]	-.12 [-.37, .13]	-.24 [-.46, -.03]	-.35 [-.73, .03]	-.16 [-.42, .10]
Work-related activities									
Paid employment at Tx (n/N and % yes)	37/55 (67.3%)	18/26 (69.2%)	19/29 (65.5%)	35/49 (71.4%)	15/22 (68.2%)	20/27 (74.1%)	31/47 (66%)	14/22 (63.6%)	17/25 (68.0%)
Work-hours missed due to health problems (mean, 95% CI)	-2.39 [-5.91, 1.13]	-4.18 [-13.04, 4.67]	-1.16 [-3.36, 1.05]	-2.80 [-6.74, 1.15]	-5.27 [-13.45, 2.90]	-1.09 [-5.42, 3.23]	-1.84 [-6.41, 2.73]	-6.18 [-13.45, 1.09]	1.14 [-4.92, 7.21]
Work-hours missed due to other reasons (mean, 95% CI)	-.84 [-7.38, 5.70]	-.11 [-1.90, 1.69]	-1.34 [-1.58, 7.90]	-1.60 [-8.32, 5.12]	1.45 [-6.71, 9.62]	-3.70 [-14.22, 6.82]	-4.33 [-1.38, 1.71]	-4.82 [-13.17, 3.53]	-4.00 [-13.25, 5.25]
Work-hours worked (mean, 95% CI)	2.74 [-2.08, 7.57]	2.36 [-6.06, 1.78]	3.00 [-3.59, 9.59]	5.32 [-.40, 11.04]	-.05 [-1.63, 1.54]	9.01 [2.24, 15.78]	5.96 [1.02, 1.89]	4.91 [-.20, 1.02]	6.68 [-1.40, 14.75]
How much did your health problems affect your productivity while you were working (0-10) (mean, 95% CI)	-.33 [-1.78, 1.11]	-2.00 [-7.36, 3.36]	.50 [-.27, 1.27]	-1.00 [-2.88, .88]	-2.25 [-8.26, 3.76]	-.38 [-2.47, 1.72]	-1.58 [-3.67, .51]	-2.25 [-7.34, 2.84]	-1.25 [-4.17, 1.67]
How much did your health problems affect your ability to perform normal activities (0-10) (mean, 95% CI)	-.42 [-1.84, 1.00]	-1.00 [-4.44, 2.44]	-.13 [-2.10, 1.85]	-1.50 [-3.52, .52]	-1.50 [-5.71, 2.71]	-1.50 [-4.50, 1.50]	-1.58 [-3.55, .38]	-1.50 [-5.71, 2.71]	-1.63 [-4.52, 1.27]
Health-related mental health									
Depression (mean, 95% CI)	.40 [-.42, 1.22]	.30 [-1.10, 1.70]	.48 [-.59, 1.55]	-.62 [-1.49, .24]	-.95 [-2.15, .25]	-.36 [-1.66, .94]	-.80 [-1.75, .15]	-.25 [-1.64, 1.14]	-1.24 [-2.60, .12]
Anxiety (mean, 95% CI)	-.69 [-1.49, .11]	-1.05 [-2.35, .25]	-.40 [-1.47, .67]	-1.11 [-1.90, -.32]	-1.75 [-2.81, -.69]	-.60 [-1.76, .56]	-1.47 [-2.38, -.55]	-1.85 [-3.38, -.32]	-1.16 [-2.34, .02]

10.2. Explanatory outcomes

10.2.1. Participant characteristics

The baseline characteristics of the study population are shown in **Error! Reference source not found.**.

We assessed if the participant characteristics affect the likelihood of being a responder, meaning "able to perform +3 1-MSTS repetitions at T2". There was no significant association between being a responder and sex (Chi-square= 1.450, df= 1, p-value= 0.229), or with having been on sickness leave (Chi-square= 0.109, df= 1, p-value= 0.741). Too few participants were admitted to the hospital and to the ICU to identify whether there is a relationship between these outcomes and being a responder. The figure below shows a scatter plot for the change in 1-MSTS repetitions between T2 and T0 and the length of long COVID symptoms. There is no linear relationship between the length of symptoms and how many extra repetitions a participant could perform compared to baseline.

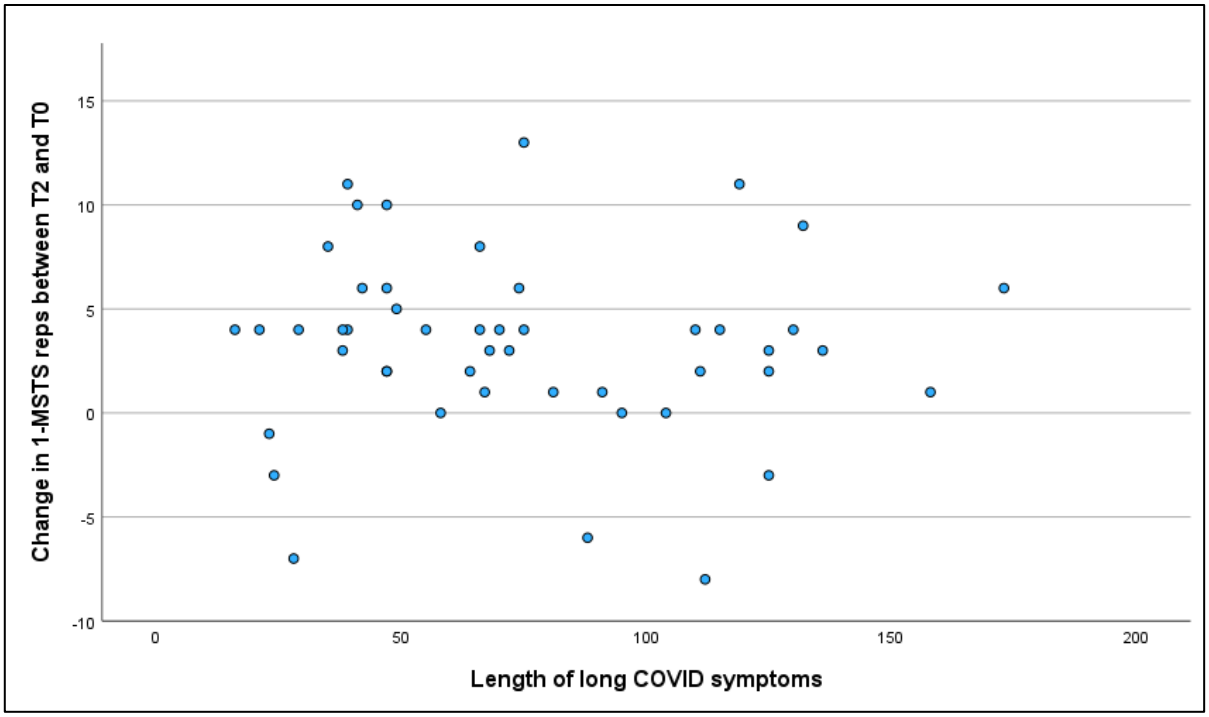


Figure 6: There is no linear relationship between the length of the long COVID symptoms (weeks) and the change in 1-MSTS repetitions. The Y-axis shows the change in 1-MSTS repetitions between T2 (12-weeks ± 7 days) and baseline. A change of ≥ 3 is considered a clinically important improvement.

10.2.2. Illness perception

The Brief Illness Perception Questionnaire (B-IPQ) was used to assess the cognitive and emotional representation of long COVID on the participants. The B-IPQ was only performed at baseline. The questionnaire consists of eight questions using a 0-to-10 response scale and an open-ended question to assess what the participants identify as the three most important causal factors in their condition. The results of the first eight questions are shown in Table 13.

The first five questions assess the cognitive illness perceptions. The first question assesses the consequences of the illness, and scored a mean of 7.28 ± 1.97, indicating that long COVID has a high impact on the participant's life. The second question assesses the timeline, and with a mean 5.46 ± 2.15, this indicates that the participants expect long COVID to last a moderately long time. Out of the 63 participants who answered this question, 4 (6.3%) answered a 10, meaning that they expect to live

with long COVID for the rest of their lives. The vast majority however, does expect that there will be an end to this condition. Question 3 evaluates how much control the participants feel they have over their condition, with a mean result of 2.50 ± 1.82, which represents little control. Of special interest to this study, question 4 evaluates how much the participants expect the treatment (in this case being the participation to the trial), to help. The mean result was 5.47 ± 2.28, indicating that the participants expected moderate positive effect. To assess if a positive expectation was related to a positive result, we performed logistic regression to evaluate the relationship between question 4 and whether participants were responders at T2 for the 1-MSTS. There was no relationship (p = 0.198), indicating that the attitude of the participants at the beginning of the trial did not influence their 1-MSTS result. The fifth question evaluates how much symptoms the participants experience, with a mean of 6.69 ± 1.63, indicating a high presence of symptoms. This also explains the high fatigue, lower quality of life, moderate functional limitations, and mild to moderate depression and anxiety that were discussed in 10.1.

Questions 6 and 8 assess the emotional representations of the condition: participants report high to very high concern (7.61 ± 1.96), and high to very high emotional effects (7.11 ± 2.05). The seventh question evaluates illness comprehensibility. The participants resort a mean of 4.42 ± 2.27, indicating moderate comprehension.

Table 13: Baseline Brief-Illness Perception Questionnaire results

	B-IPQ questions (scale)	Total
1	How much does your illness affect your life? (0 = no affect at all, 10 = severely affects my life)	7.28 ± 1.97
2	How long do you think your illness will continue? (0 = a very short time, 10 = forever)	5.46 ± 2.15
3	How much control do you feel you have over your illness? (0 = absolutely no control, 10 = extreme amount of control)	2.50 ± 1.82
4	How much do you think your treatment can help your illness? (0 = not at all, 10 = extremely helpful)	5.47 ± 2.28
5	How much do you experience symptoms from your illness? (0 = no symptoms at all, 10 = many severe symptoms)	6.69 ± 1.63
6	How concerned are you about your illness? (0 = not concerned at all, 10 = extremely concerned)	7.61 ± 1.96
7	How well do you feel you understand your illness? (0 = don't understand at all, 10 = understand very clearly)	4.42 ± 2.27
8	How much does your illness affect you emotionally? (E.g., does it make you angry, scared, upset or depressed?)(0 = not at all affected emotionally, 10 = extremely affected emotionally)	7.11 ± 2.05

When asked to identify the three most important causal factors in their condition, the participants mentioned the following reasons:

- SARS-CoV-2 infection itself
- High physical and/or mental load (e.g., stress, fatigue, busy job, family, pressure to perform)

- Pre-existing medical issues (e.g., medical history, medication use, nutritional deficits)
- Faulty pandemic policy (e.g., inadequate workplace prevention, other individuals not following hygiene measures, lack of knowledge on long COVID thus incorrect treatment)
- Vaccination against SARS-CoV-2
- Bad luck

10.2.3. Adherence and compliance

Physiotherapy and exercise sessions

In the protocol, we described compliance as “the ratio of the total training intensity*duration (recorded in the logbooks) versus the prescribed total training intensity*duration, multiplied by 100”. Because the majority participants either did not submit or incorrectly filled in the physical activity diaries (see Protocol adherence in 5.4.1), it was impossible to calculate the physical activity compliance. In addition, it is difficult to do this calculation since the rehabilitation of long COVID is individually and symptom titrated, and therefore no "one fits all" principle can be used. Training focuses on the participant's independence and pacing of the PESE, and consequently the activities the participant schedules in his/her day/week, either physical activities or physiotherapy sessions. Thus, we cannot determine a "prescribed" total training intensity*duration, as each participant is approached individually, and the rehabilitation progression is based on the symptoms experienced by the participant.

Additionally, when we asked 35 participants (54%) if they continued with physiotherapy beyond the 12 weeks of the intervention, 77% (73% in the control group and 80% in the intervention group), did continue after T2. During the Trial Steering Committee of 28-Oct-2022, we discussed whether this would compromise the results of the trial. We concluded that it would be unethical to demand participants to stop attending the physiotherapy sessions if it helped them to manage their symptoms, as it is considered the standard of care. Therefore, we recorded some additional information on the physiotherapy sessions in some participants during the feedback consultation (see Table 14).

Generally, 27 participants (42%, 11 in the control group, 16 in the intervention group), reported that they used 14 (25^{th}-75^{th} percentile: 12-18) out of the 18 prescribed sessions before the end of the intervention at T2. The amount of sessions was slightly higher in the intervention group (15 vs. 12 sessions in the control group). These sessions consisted mostly out of resistance training, breathing exercises, other (meaning cardio and stability) and relaxation exercises. However, because of the low number of participants who provided this information, these results can be biased. In a future qualitative study in both participants and the physiotherapists from the intervention group, we aim to gather more information on the nature of the physiotherapy sessions.

Table 14: Physiotherapy sessions

	Total	CG	IC
Number of physiotherapy sessions between T0 and T2 (Median (25^{th}-75^{th} percentile))	n = 27 14 (12-18)	n = 11 12 (12 -18)	n = 16 15 (12 -18)
What kind of therapy did you receive?	n = 26	n = 11	n = 15
Breathing exercises (% yes)	77	55	93

Relaxation exercises (% yes)	23	50	40
Resistance exercises (% yes)	89	83	93
Other (% yes)	46	62	31
Continuation physiotherapy after T2 (% yes)	n = 35 77	n = 15 73	n = 20 80

To assess if the number of physiotherapy sessions a participant received was related to a positive result, we performed logistic regression to evaluate the relationship between the amount of sessions by T2 and whether participants were responders at T2 for the 1-MSTS. There was no significant relationship (p = 0.430). As mentioned earlier, we do not have sufficient information to interpret why this is not the case, as we only have information on the contents of the physiotherapy from 27 out of the 65 participants.

Nutrition

The adherence of the nutritional counselling was described in detail in 5.4.1.

Similarly, we assessed whether the number of teleconsultations with a study dietitian was related to being a responder at T2 for the 1-MSTS, using logistic regression. There was no significant relationship (p = 0.188).

10.2.4. Dyspnoea

To assess the perceived respiratory disability, we used the modified Medical Research Council (mMRC) Dyspnoea questionnaire. As the mMRC dyspnoea scale allows participants to indicate the extent to which their breathlessness affects their mobility, we evaluated if dyspnoea explains the functional performance results (1-MSTS). The presence of dyspnoa at baseline was not related to being a reponder at T2 (Chi-square= 2.780, df = 1, p-value = 0.95), and neither was dyspnoea at T2 (Chi-square: 3.284, df = 1, p-vaue = 0.070). However, for some participants, the dyspnoea was not triggered by physical activity, but could happen at rest, while sleeping, or be brought on by emotional exertion, meaning that the mMRC dyspnoea scale might not be specific enough to accommodate for dyspnoea that is not linked to physical exertion. To mitigate this, we added the option “other” to the grade scale.

Table 15 shows the results. The majority of participants (87.9% in the control group and 71.0 % in the intervention group) indicated at baseline that they experience shortness of breath. The proportion of the participants with dyspnoea reduced throughout the duration of the study in both groups, although proportionally more in the control group, especially at T3 (-19.2% in the control group compared to -11.0% in the intervention group). There was no clear improvement nor decline in either group based on the dyspnoea grades.

10.2.5. Activities of daily living

To confirm the health-related quality of life (EQ-5D-5L) and post-COVID-19 functional status (PCFS), the Barthel Index was used. The Barthel Index assesses the degree of independence while performing activities of daily living (ADL), including feeding, functional mobility, personal care, getting on and off the toilet, bathing, walking on a level surface or propelling a wheelchair, using stairs, (un)dressing, and bowel and bladder continence. A higher score indicates a higher independence. The baseline mean

score was 98.92 ± 3.48, indicating that the study population can independently perform the activities of daily living.

NOTE: During the study visits, many participants noted that their answers needed more nuance, while the Barthel Index uses a dichotomous scaling (dependent – independent). For example, while most participants can bathe independently, many of them have reduced the frequency of their showers, they will take a pause in between washing their hair and body, or they will reduce any other activities on bathing days. Similarly, most participants can walk independently, but they avoid any household tasks that involve walking, such as grocery shopping or running errands, as those activities can heavily affect their symptoms. Additionally, because of the nature of the study, the results from our population are biased, as individuals with more severe symptoms who are more dependent on others for the ADL did not participate.

10.2.6. Physical performance

To confirm the results of the 1-MSTS, multiple physical assessments were performed. **Error! Reference s ource not found.** shows the baseline results of the 6-MWT, the muscle strength tests and the handgrip strength test. **Error! Reference source not found.** shows the changes of these assessments throughout t he duration of the study. Both tables are divided into the results for the female and male participants.

6-Minute walk test

At baseline, participants were able to walk on average 536.30 ± 96.73 meters in six-minutes. Compared to the standards in the general population of 581.4 ± 66.5 m (range 383–800 m) for females and 608.7 ± 80.1 m (range 410–875 m) for males, they had a had a slightly lower performance than average [43]. Bohannon and Crouch concluded that a change of 14.0 to 35.5 meters may be clinically important across multiple patient groups [44]. **In our study population, we show a significant change within the intervention group from T1 onwards** (+13.65 [95% CI: 1.74; 25.56] at T1, +21.26 [95% CI: 5.13; 37.39] at T2, and +34.79 [95% CI: 15.89; 53.70] at T3). In the participants of the control group, the changes throughout the study were on average neither clinically important nor statistically significant**.** This confirms the promising positive effect in the intervention group on functional performance that was shown with the 1-MSTS tests results. The greater effect at T3 compared to T2 also strengthens the argument for a longer interventional period.

Muscle strength

At baseline, isometric muscle strength of the participants was measured using a MicroFet 2 hand-held dynamometer (Hogan Health Industries, Inc. 8020 South 1300 West, West Jordan, USA). The strength on the right side was usually higher compared to the left where this was also the dominant side.

Unfortunately, there are no standard values available for the Belgian population. In general, both intervention and control group show positive evolution in isometric muscle strength compared to baseline, but the differences were **not significant** for all muscle groups. Significant improvement is seen at the end of intervention (T2) for hip flexion and knee extension on both sides and right shoulder abduction, which is maintained at follow up (T3) except for knee extension. At follow-up we see also significant improvement of left shoulder abduction strength.

Handgrip strength

Of the 64 participants who performed the handgrip strength test at baseline, 59 (90.8%) were right-handed and 5 (7.7%) were left-handed. Mean maximal force at baseline was 72.58 ± 20.24 in the control group and 79.29 ± 28.19 in the intervention group.

In our study, the participants show a positive evolution in handgrip strength in both control and intervention group, but the difference was **not significant** compared to baseline.

10.2.7. Nutritional and metabolic parameters

Table 18**Error! Reference source not found.** shows the results for the nutritional parameters.

The Resting Energy Expenditure (REE) was measured by Indirect Calorimetry (IC) in 64 participants and calculated using the WHO formula for one participant. The mean REE was 1823 ± 365 kcal/day or 24 ± 4 kcal/kg/day. As mentioned earlier, to assess the Total Energy Expenditure (TEE), the REE was multiplied by a Physical Activity Level (PAL). Participants were asked to rank their physical activity level (PAL) as one of the following: inactive (<1.4) / sedentary (1.4) / moderately active (1.6)/ active (1.8) / very active (>1.8), in accordance with the Belgian High Health Council [30]. The mean PAL was 1.6 ± 0.1 (i.e., moderately active) with a range between 1.3 and 2.0. After comparison with the physical activity in the diaries, we conclude that these answers are not accurate. However, it is not possible to correct these PAL values, as the physical activity diaries were incomplete. Therefore, the TEE values are overestimated, with a mean of 2848 ± 647 kcal/day. This leads to a biased **energy-feeding adequacy (EFA)**, defined as energy intake/TEE. **The mean EFA was 0.69 ± 0.21,** but in reality, it is expected to be higher.

On the other hand, if we defined the EFA as the energy intake/REE, **only 50% of participants had an EFA ≥ 1, meaning that their energy intake covered their resting energy expenditure**, not taking into account any additional energetic need due to physical activity. Besides the caloric intake, the quality of the eating pattern was also of interest, more specifically the macronutrient intake. The mean protein intake was 1.01 ± 0.37 g/kg/day. Around half of the participants (54.8%) had a protein intake within the guidelines of minimally 0.83 g/kg/day and maximally 1.5 g/kg/day. The carbohydrate and lipid intake are expressed in En%, meaning the percentage of the total energy intake from the respective macronutrient. The mean carbohydrate intake was 43 ± 7 En%. Only 16% of participants had a carbohydrate within the High Health Council's guideline of 50-55 En%, with the majority consuming less. Furthermore, the mean lipid intake was 36 ± 7 En%, with 41.9% of participants with an intake within the guidelines of ≥ 20 En% and ≤ 35 En%. **We can conclude that the nutritional intake of a significant part of the UNLOCK population at baseline was disbalanced in macronutrient intake and the total energy intake was insufficient.**

After the end of the nutritional intervention at T2, there were no noticeable differences in mean energy intake or macronutrient intake compared to baseline. We expected that the energy and macronutrient intake of participants in the control group (who did not receive individualized nutritional counselling) would not specifically improve nor deteriorate. However, **it was expected that the intake of participants in the intervention group would become more consistent with the guidelines**, as the dietitians guided these participants during weekly tele-consultations. **This positive evolution was not observed**, as shown in Figure 7. The percentage of participants whose energy or macronutrient intake agreed with the guidelines does not show a clear linear relationship with the presence of a nutritional intervention. Based on logistic regression, the total number of teleconsultations with a dietitian was not related to having an EFA based on REE ≥ 1 (p = 0.488), protein intake ≥ 0.83 g/kg/day ≤ 1.5 g/kg/day

(p = 0.927), carbohydrate intake between 50-55 En% (p = 0.753), or a lipid intake ≥ 20 ≤ 35 En% (p = 0.762). Nutritional diaries can be inaccurate, as they are susceptible to different kinds of bias, such as social desirability bias (e.g., the underreporting of foods that may seem "unhealthy" or overreporting of foods that seem "healthy"), inaccurate estimations of portion sizes, forgetting to add ingredients etc. To understand better why the nutritional intervention did seemingly not have an influence on the eating pattern of the participants, an additional qualitative study will be performed. We will identify the facilitators and barriers of the nutritional intervention, from the perspectives of both participants and the dietitians. This will provide important information for the development of a large-scale RCT and for the intervention's implementation. This additional study falls outside the scope of this clinical study report.

We hypothesized that the Resting Energy Expenditure (REE), the energy feeding adequacy and macronutrient intake could explain both functional performance (1-MSTS) and fatigue (MFI-20). We assessed the correlation between these outcomes (Table 19). There were no correlations between REE and functional performance or fatigue. There was **a significant negative correlation between the EFA based on the REE at baseline and the baseline general fatigue (r = -0.293, p = 0.021) and physical fatigue** (r = -0.351, p = 0.005). The baseline carbohydrate intake was negatively correlated with general fatigue (r = -0.334, p = 0.008), physical fatigue (r = -0.454, p < 0.001) and reduced activity (r = -0.264, p = 0.038). The baseline lipid intake was correlated with general fatigue (r = 0.374, p = 0.003). This indicates that a better feeding adequacy, mostly from carbohydrates and lipids (which are also the biggest contributors to total kcal intake) was linked to lower fatigue at the beginning of the trial. Interestingly, these correlations were not present at T2. The change in functional performance (difference in 1-MSTS repetitions between T2 and T0) was however linked with baseline protein intake (r = 0.333, p = 0.019) and all nutritional intake outcomes at T2, including EFA based on REE (0.397, p = 0.005), protein intake (r = 0.408, p = 0.004), carbohydrate intake (r = 0.461, p < 0.001), and lipid intake (r = 0.337, p = 0.019). This indicates that the baseline protein intake was positively linked to the changes in functional performance at T2, and that a higher energy, protein, carbohydrate and lipid intake at T2 were linked to a higher improvement in functional performance. Although this is a pilot trial, these results are promising.

To better interpret the impact of nutrition on the participant's body composition, we performed a bioelectrical impedance analysis (BIA). At baseline, the mean phase angle (PhA) was 5.9 ± 0.6. A higher PhA is an indicator of better cellular health (cell mass, membrane integrity, and cell function), and of nutritional and hydric status [47-49]. This is slightly lower compared to the healthy population, i.e., a mean of 6.5 to 7.0 in adult males and 5.6 to 6.3 in adult females, depending on their age [50]. Using the BIA, the Fat Mass Index (FM/height²) and Fat Free Mass Index (FFM/height²) were calculated for the study participants. To assess the double burden of excess FM and low FFM, the mean FM/FFM ratio was also calculated. At baseline, participants had a FMI of 8.2 ± 2.8 kg/m² and a FFMI of 17.6 ± 2.3 kg/m². This is slightly lower to the values in the general population, i.e. 9.7 ± 4.1 kg/m² and 16.7 ± 2.2 kg/m² [51]. The FM/FFM ratio in UNLOCK participants was 0.47 ± 0.15, which compares to the general male population [51]. All of these results indicate **that at baseline, the UNLOCK population had a body composition that corresponds with the general population. None of the body composition outcomes changed throughout the duration of the study**.

Additionally, we wanted to assess if the fat mass/fat-free mass (FM/FFM) ratio explains functional performance (1-MSTS) and the REE. We also assessed if the phase angle (PhA) explains the functional

performance. There were no significant correlations between FM/FFM or PhA and functional performance (Table 20).

Table 15: Dyspnoea throughout the duration of the study

	T0			T1-T0			T2-T0			T3-T0		
	Total n = 64	**CG** n = 33	**IG** n = 31	Total n = 53	CG n = 25	IG n = 28	Total n = 49	CG n = 22	IG n = 27	Total n = 47	CG n = 22	IG n = 25
Dyspnoea												
% yes	79.5	87.9	71	67.9 (-11.6%)	72 (-15.9%)	64.3 (-6.5%)	63.3 (-16.2%)	72.7 (-15.2%)	55.6 (-15.4%)	63.8 (-15.7%)	68.2 (-19.2%)	60 (-11.0%)
Dyspnoea only with strenuous exercise (% yes)	3.9	3.4	4.5	8.3 (+4.4%)	0 (-3.4%)	16.7 (+12.2%)	6.5 (+2.6%)	6.3 (+2.9%)	6.7 (+2.2%)	16.7 (+12.8%)	13.3 (+9.9%)	20 (+15.5%)
Dyspnoea when hurrying or walking up a slight hill (% yes)	58.8	51.7	68.2	50 (-8.8%)	55.6 (+3.9%)	44.4 (-23.8%)	45.2 (-13.6%)	43.8 (-7.9%)	46.7 (-21.5%)	30 (-28.8%)	33.3 (-18.4%)	26.7 (-41.5%)
I walk slower than people of the same age because of dyspnoea or have to stop for breath when walking at own pace (% yes)	19.6	24.1	0	19.4 (-0.2%)	22.2 (-1.9%)	16.7 (+16.7%)	29 (+9.4%)	37.5 (+13.8%)	20 (+20.0%)	30 (+10.4%)	33.3 (+9.2%)	26.7 (+26.7%)
I stop for breath after walking 100 m or after a few minutes (% yes)	5.9	10.3	13.6	5.6 (-0.3%)	5.6 (-4.7%)	5.6 (-8.0%)	3.2 (-2.7%)	0 (-10.3%)	6.7 (-6.9%)	6.7 (+0.8%)	13.3 (+3.0%)	0.0 (-13.6%)
Too dyspneic to leave house or breathless when dressing (% yes)	9.8	10.3	9.1	8.3 (-1.5%)	11.1 (+0.8%)	5.6 (-3.5%)	6.5 (-3.3%)	6.3 (-4.0%)	6.7 (-2.4%)	6.7 (-3.1%)	0 (-10.3%)	13.3 (+4.2%)
Other (% yes)	2	0	4.5	8.3 (+6.5%)	5.6 (+5.6%)	11.1 (+6.6%)	9.7 (+7.7%)	6.3 (+6.3%)	13.3 (+8.8%)	10 (+8.0%)	6.7 (+6.7%)	13.3 (+8.8%)

CG: control group, IG: intervention group

Table 16: Baseline results of the physical assessments (6-minute walk test, muscle strength, handgrip strength)

	Total	CG	IG
6-MWT distance (meters) (mean ± SD)	536.30 ± 96.73	530.56 ± 113.87	542.42 ± 75.79
Muscle strength			
Right shoulder abduction (N)(mean ± SD)	129.87 ± 58.03	126.03 ± 53.13	133.97 ± 63.47
Left shoulder abduction (N)(mean ± SD)	130.37 ± 52.08	127.43 ± 48.49	133.51 ± 56.29
Right elbow flexion (N)(mean ± SD)	152.27 ± 59.48	149.88 ± 56.66	154.82 ± 63.19
Left elbow flexion (N)(mean ± SD)	157.15 ± 58.35	156.22 ± 58.12	158.15 ± 59.54
Right wrist extension (N)(mean ± SD)	50.96 ± 22.87	49.65 ± 22.02	52.36 ± 24.04
Left wrist extension (N)(mean ± SD)	47.14 ± 21.16	46.16 ± 22.56	48.20 ± 19.88
Right hip flexion (N)(mean ± SD)	113.11 ± 46.63	107.20 ± 45.31	119.40 ± 47.91
Left hip flexion (N)(mean ± SD)	108.55 ± 43.30	105.47 ± 43.47	111.82 ± 43.61
Right knee extension (N)(mean ± SD)	258.22 ± 127.65	240.45 ± 120.91	277.14 ± 133.82
Left knee extension (N)(mean ± SD)	225.68 ± 105.57	218.49 ± 102.98	233.59 ± 109.55
Right ankle dorsiflexion (N)(mean ± SD)	119.44 ± 52.74	117.50 ± 59.13	121.50 ± 45.86
Left ankle dorsiflexion (N)(mean ± SD)	119.74 ± 50.59	122.07 ± 58.12	117.26 ± 41.94
Handgrip strength			
Maximal force (Kpa) (mean ± SD)	75.83 ± 24.45	72.58 ± 20.24	79.29 ± 28.19
Fatigue resistance (seconds) (mean ± SD)	37.58 ± 22.70	41.31 ± 28.43	33.62 ± 13.72

6-MWT: 6-minute walk test, CG: control group, IG: intervention group, Kpa: kilopascal, N: Newton, SD: standard deviation

Table 17: Changes in physical assessments (6-minute walk test, muscle strength, handgrip strength) throughout the duration of the study

	T1-T0			T2-T0			T3-T0		
	Total mean [95% CI]	CG mean [95% CI]	IG mean [95% CI]	Total mean [95% CI]	CG mean [95% CI]	IG mean [95% CI]	Total mean [95% CI]	CG mean [95% CI]	IG mean [95% CI]
6-MWT distance (meters)	10.95 [-0.55; 22.45]	8.14 [-12.74; 29.02]	**13.65 [1.74; 25.56]**	13.40 [-2.04; 28.84]	3.75 [-25.56; 33.06]	**21.26 [5.13; 37.39]**	**23.32 [6.06; 40.57]**	10.80 [-19.67; 41.26]	**34.79 [15.89; 53.70]**
Muscle strength									
Right shoulder abduction (N)	5.68 [-1.78; 13.14]	6.59 [-4.98; 18.17]	4.83 [-5.49; 15.16]	**11.31 [1.62; 21.00]**	8.39 [-10.27; 27.06]	**13.67 [3.39; 23.94]**	**15.49 [5.36; 25.63]**	9.21 [-8.00; 26.42]	**21.02 [8.65; 33.39]**
Left shoulder abduction (N)	5.08 [-2.30; 12.46]	1.39 [-11.24; 14.03]	8.49 [-0.25; 17.23]	**9.39 [0.20; 18.58]**	5.87 [-8.27; 20.01]	12.23 [-0.61; 25.08]	**13.76 [5.59; 21.94]**	4.65 [-8.32; 17.61]	**21.79 [11.72; 31.86]**
Right elbow flexion (N)	0.23 [-6.90; 7.37]	-0.44 [-13.22; 12.34]	0.85 [-7.09; 8.80]	-0.10 [-10.61; 10.40]	1.27 [-16.79; 19.32]	-1.21 [-14.57; 12.14]	3.25 [-5.51; 12.01]	-1.39 [-16.41; 13.64]	7.33 [-3.30; 17.97]
Left elbow flexion (N)	3.75 [-4.04; 11.53]	-0.47 [-14.07; 13.13]	7.81 [-0.81; 16.42]	1.92 [-7.79; 11.64]	-1.63 [-21.23; 17.98]	4.79 [-4.34; 13.92]	3.13 [-6.31; 12.58]	-4.00 [-19.24; 11.24]	9.41 [-2.70; 21.53]
Right wrist extension (N)	**4.69 [0.43; 8.94]**	2.45 [-4.85; 9.75]	**6.75 [1.73; 11.77]**	3.54 [-2.49; 9.57]	-0.05 [-7.21; 7.12]	6.42 [-3.12; 15.95]	2.10 [-2.33; 6.52]	1.67 [-6.49; 9.84]	2.47 [-2.44; 7.37]
Left wrist extension (N)	**4.88 [0.89; 8.86]**	4.22 [-3.01; 11.45]	**5.48 [1.16; 9.80]**	**5.19 [0.16; 10.23]**	2.11 [-5.32; 9.54]	**7.78 [0.62; 14.94]**	3.19 [-1.09; 7.46]	1.22 [-5.34; 7.79]	5.07 [-0.87; 11.00]
Right hip flexion (N)	**8.38 [2.45; 14.30]**	**10.73 [0.81; 20.64]**	6.21 [-1.15; 13.56]	**11.93 [5.00; 18.85]**	5.04 [-3.77; 13.86]	**17.49 [7.17; 27.80]**	**15.01 [5.61; 24.41]**	6.52 [-3.53; 16.58]	**22.48 [7.08; 37.87]**
Left hip flexion (N)	**7.87 [1.19; 14.54]**	5.06 [-4.96; 15.08]	**10.47 [1.03; 19.91]**	**11.34 [4.93; 17.75]**	4.58 [-5.73; 14.90]	**16.80 [8.75; 24.85]**	**13.42 [5.94; 20.90]**	8.73 [-0.72; 18.19]	**17.54 [5.80; 29.27]**
Right knee extension (N)	-2.29 [-17.81; 13.23]	5.15 [-19.95; 30.26]	-9.1 [-29.27; 10.91]	18.96 [-0.90; 38.82]	4.71 [-24.35; 33.77]	**30.46 [2.33; 58.60]**	14.08 [-7.09; 35.25]	12.29 [-18.63; 43.21]	15.65 [-15.53; 46.83]
Left knee extension (N)	7.07 [-6.87; 21.01]	9.03 [-12.90; 30.97]	5.18 [-13.74; 24.10]	**26.71 [5.12; 48.30]**	26.34 [-12.48; 65.17]	**27.01 [1.41; 52.62]**	21.35 [-2.32; 45.02]	16.86 [-22.05; 55.78]	25.46 [-5.47; 56.39]
Right ankle dorsiflexion (N)	5.71 [-5.96; 17.38]	8.70 [-8.46; 25.86]	3.05 [-13.89; 19.99]	9.21 [-5.84; 24.27]	7.44 [-13.38; 28.27]	10.64 [-12.06; 33.34]	12.51 [-0.98; 26.00]	5.80 [-15.44; 27.05]	18.41 [0.15; 36.67]
Left ankle dorsiflexion (N)	3.06 [-8.84; 14.97]	1.78 [-15.66; 19.22]	4.25 [-13.16; 21.66]	4.40 [-11.02; 19.83]	-3.90 [-26.94; 19.13]	11.11 [-10.74; 32.96]	11.04 [-2.67; 24.74]	-3.03 [-24.13; 18.07]	**23.42 [5.65; 41.19]**
Handgrip strength									
Maximal force (Kpa)	-1.33 [-3.85; 1.20]	-1.88 [-5.17; 1.41]	-0.81 [-4.81; 3.18]	-0.10 [-3.07; 2.87]	-0.59 [-5.11; 3.93]	0.30 [-3.91; 4.51]	-0.70 [-3.94; 2.53]	-3.00 [-8.47; 2.47]	1.32 [-2.61; 5.25]
Fatigue resistance (seconds)	5.98 [-0.27; 12.23]	10.05 [-0.25; 20.36]	2.21 [-5.52; 9.95]	6.46 [-1.30; 14.22]	3.06 [-11.43; 17.55]	**9.23 [0.67; 17.78]**	3.87 [-3.49; 11.24]	3.20 [-7.92; 14.31]	4.47 [-6.09; 15.04]

6-MWT: 6-minute walk test, 95% CI: 95% confidence interval, CG: control group, IG: intervention group, Kpa: kilopascal, N: Newton, SD: standard deviation

Table 18: Nutritional outcomes (energy expenditure, intake, bioelectrical impedance analysis) throughout the duration of the study

	T0			T1			T2			T3		
	Total	CG	IG	Total	CG	IG	Total	CG	IG	Total	CG	IG
Energy expenditure												
REE kcal/day (mean ± SD)	1823 ± 365	1802 ± 364	1845 ± 370	1853 ± 372	1842 ± 369	1864 ± 381	1876 ± 359	1831 ± 331	1913 ± 383	1890 ± 394	1895 ± 455	1886 ± 340
REE kcal/kg/day (mean ± SD)	24 ± 4	24 ± 3	24 ± 4	25 ± 4	24 ± 4	25 ± 5	25 ± 4	24 ± 3	25 ± 5	25 ± 4	24 ± 3	25 ± 5
TEE kcal/day (mean ± SD)	2848 ± 647	2812 ± 704	2888 ± 588	2924 ± 676	2973 ± 753	2880 ± 609	3020 ± 692	3001 ± 758	3035 ± 647	3044 ± 718	3095 ± 882	2998 ± 550
Intake												
EFA based on TEE (mean ± SD)	0.69 ± 0.21	0.69 ± 0.22	0.68 ± 0.20	0.69 ± 0.18	0.65 ± 0.16	0.72 ± 0.20	0.66 ± 0.22	0.65 ± 0.24	0.68 ± 0.20	0.63 ± 0.27	0.61 ± 0.24	0.65 ± 0.30
EFA based on REE (mean ± SD)	1.06 ± 0.31	1.07 ± 0.31	1.05 ± 0.32	1.08 ± 0.27	1.02 ± 0.24	1.12 ± 0.29	1.07 ± 0.36	1.03 ± 0.36	1.10 ± 0.36	1.08 ± 0.36	1.04 ± 0.33	1.13 ± 0.39
% EFA based on REE ≥ 1	50.00	54.80	45.20	41.90	50.00	63.00	50.00	42.90	55.60	50.00	42.90	56.50
Protein intake (g/kg/day) (mean ± SD)	1.01 ± 0.37	0.99 ± 0.33	1.03 ± 0.40	1.06 ± 0.37	0.92 ± 0.21	1.17 ± 0.43	1.06 ± 0.45	0.98 ± 0.40	1.12 ± 0.49	1.00 ± 0.35	0.97 ± 0.32	1.02 ± 0.38
% Protein intake ≥ 0.83 g/kg/day and ≤ 1.5 g/kg/day	54.80	51.60	58.10	57.40	65.00	74.10	52.10	52.40	51.90	52.30	52.40	52.20
Carbohydrate intake (En%) (mean ± SD)	0.43 ± 0.07	0.44 ± 0.05	0.42 ± 0.08	0.43 ± 0.06	0.43 ± 0.05	0.43 ± 0.06	0.45 ± 0.09	0.45 ± 0.08	0.45 ± 0.09	0.43 ± 0.09	0.41 ± 0.10	0.44 ± 0.08
% CHO intake ≥ 50 and ≤ 55 EN%	16.10	12.90	19.40	70.20	10.00	7.40	16.70	14.30	18.50	11.40	4.80	17.40
Lipid intake (En%) (mean ± SD)	0.36 ± 0.07	0.36 ± 0.06	0.37 ± 0.07	0.37 ± 0.06	0.38 ± 0.06	0.36 ± 0.06	0.36 ± 0.06	0.35 ± 0.07	0.37 ± 0.05	0.38 ± 0.08	0.39 ± 0.08	0.37 ± 0.07
% Lipid intake ≥ 20 and ≤ 35 EN%	41.90	48.60	35.50	8.50	20.00	33.30	29.20	28.60	29.60	38.60	42.90	34.80
Bioelectrical Impedance Analysis												
Phase angle (mean ± SD)	5.9 ± 0.6	6.0 ± 0.6	5.9 ± 0.6	5.9 ± 0.6	5.9 ± 0.5	5.9 ± 0.7	5.9 ± 0.6	5.8 ± 0.5	5.9 ± 0.6	6.0 ± 0.5	5.9 ± 0.5	6.1 ± 0.5
FMI (kg/m²) (mean ± SD)	8.2 ± 2.8	8.3 ± 2.4	8.0 ± 3.2	8.0 ± 2.7	8.3 ± 2.3	7.7 ± 3.0	8.2 ± 2.7	8.4 ± 2.3	8.1 ± 3.1	8.4 ± 2.7	8.5 ± 2.3	8.4 ± 3.0
FFMI (kg/m²) (mean ± SD)	17.6 ± 2.3	17.7 ± 2.4	17.4 ± 2.2	17.6 ± 2.2	17.8 ± 2.4	17.4 ± 2.0	17.6 ± 2.4	17.6 ± 2.6	17.6 ± 2.3	17.8 ± 2.4	18.1 ± 2.6	17.6 ± 2.3
FM/FFM ratio (mean ± SD)	0.47 ± 0.15	0.47 ± 0.13	0.46 ± 0.18	0.46 ± 0.15	0.47 ± 0.13	0.44 ± 0.17	0.47 ± 0.16	0.49 ± 0.15	0.46 ± 0.18	0.48 ± 0.15	0.48 ± 0.13	0.48 ± 0.17

CG: control group, EFA: Energy Feeding Adequacy, En%: energy percent (percentage of the total energy intake from the respective macronutrient), IG: intervention group, REE: Resting Energy Expenditure, SD: standard deviation, TEE: Total Energy Expenditure

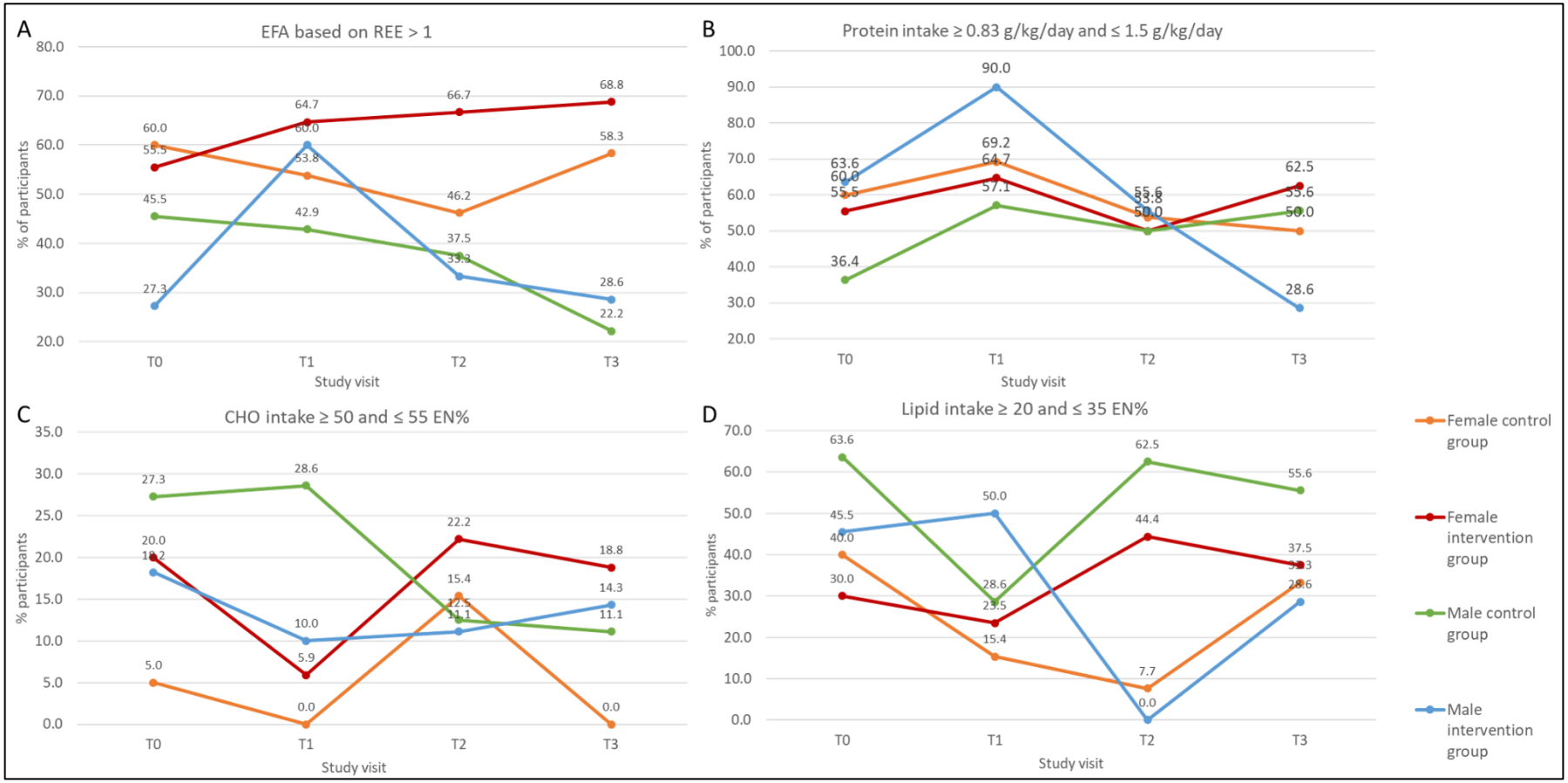


Figure 7: Percentage of participants with an energy, protein, carbohydrate and lipid intake within the guidelines throughout the study.

A. Percentage of participants with an energy-feeding adequacy (EFA) based on the Resting Energy Expenditure (REE) ≥ 1. **B.** Percentage of participants with a protein intake of minimally 0.83 g/kg body weight/day and maximally 1.5 g/kg body weight/day. **C.** Percentage of participants with a carbohydrate (CHO) intake ≥ 50 and ≤ 55 energy percent (En%: percentage of the total energy intake from the respective macronutrient). **D.** Percentage of participants with a lipid intake ≥ 20 and ≤ 35 En%.

Table 19: Correlations between nutritional intake and fatigue (MFI-20) and functional performance (1-MSTS)

	T0 REE	T0 EFA (REE)	T0 Protein intake	T0 CHO intake	T0 Lipid Intake	T2 REE	T2 EFA (REE)	T2 Protein intake	T2 CHO intake	T2 Lipid Intake
T0 MFI General fatigue	-0.048	-0.293*	-0.237	-0.334**	-0.374**	/	/	/	/	/
T0 MFI phyiscal fatigue	-0.031	-0.351**	-0.189	-0.454**	-0.25	/	/	/	/	/
T0 MFI Reduced activity	0.029	-0.214	-0.072	-0.264*	-0.072	/	/	/	/	/
T0 MFI Reduced motivation	0.142	-0.073	-0.152	0.028	-0.015	/	/	/	/	/
T0 MFI Mental fatigue	0.096	-0.246	-0.212	-0.137	-0.148	/	/	/	/	/
T2 MFI General fatigue	0.048	-0.102	-0.081	-0.139	-0.054	0.078	-0.077	0.016	-0.033	-0.059
T2 MFI phyiscal fatigue	0.007	-0.189	-0.151	-0.185	-0.165	0.012	0.051	0.072	0.026	0.103
T2 MFI Reduced activity	-0.003	0.016	0.124	-0.079	-0.016	0.115	-0.005	0.166	0.084	0.022
T2 MFI Reduced motivation	-0.078	0.056	0.33	0.019	-0.031	0.097	-0.025	0.058	0.051	-0.027
T2 MFI Mental fatigue	0.172	-0.106	-0.008	-0.05	0.098	0.245	-0.022	0.062	0.085	0.138
T2 1-MSTS change compared to T0	0.134	0.062	0.333*	0.183	0.026	0.135	0.397**	0.408**	0.461**	0.337*

*. Correlation is significant at the 0.05 level (2-tailed), **. Correlation is significant at the 0.01 level (2-tailed). *1-MSTS: 1-minute sit-to-stand test, CHO: carbohydrate, MFI: Multidimensional Fatigue Inventory, REE: Resting Energy Expenditure, T0: baseline, T2: 12 weeks ± 7 days.*

Table 20: correlations between Fat Mass/Fat-free Mass (FM/FFM) ratio and phase angle (PhA), and functional performance (1-MSTS)

	T0 FM/FFM	T0 PhA	T2 FM/FFM	T0 PhA
T2 1-MSTS change compared to T0	-0.097	0.013	-0.044	0.138

1-MSTS: 1-minute sit-to-stand test, T0: baseline, T2: 12 weeks ± 7 days.

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