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Effects of a symptom-titrated exercise program on fatigue and quality of life in people with post-COVID condition – a randomized controlled trial

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Fatigue is the most prevalent symptom within the post-COVID condition (PCC). Furthermore, many patients suffer from decreased physical performance capacity and post-exertional malaise. Although exercise has been proposed as an effective therapeutic strategy for PCC, there is limited evidence on individualised and symptom-titrated exercise interventions in patients with fatigue and PEM. Therefore, we conducted a multi-centre randomised controlled trial to investigate the effectiveness of an individualised and symptom-titrated exercise program. We measured fatigue, health-related quality of life, hand-grip strength, endurance capacity and PEM before and after the 10-week intervention. A total of 118 individuals with PCC were included in the final intention-to-treat analysis. All tests and training sessions took place in commercial fitness and health facilities. We found significant effects on fatigue severity, health-related quality of life and physical performance capacity. Adjusting the individual exercise load to daily fatigue has proven to be an effective and safe strategy in PCC patients with fatigue. Under the guidance of qualified professionals and by utilising symptom-titrated training recommendations, commercial fitness and health facilities present an appropriate setting for outpatient exercise rehabilitation in PCC.

Keywords SARS-CoV-2, Coronavirus, PCC, COVID-19, Exercise, Long COVID

Abbreviations

BFI	Brief fatigue inventory
CON	Control group
CST	Chester step test
DSQ-PEM	DePaul symptom questionnaire-PEM
F_{max}	Maximum hand grip strength
F_{mean}	Mean hand grip strength
FSS	Fatigue severity scale
HGS	Hand grip strength
HR	Heart rate
HRQoL	Health-related quality of life
INT	Intervention group
ME/CFS	Myalgic encephalomyelitis/chronic fatigue syndrome
PCC	Post-COVID condition
PEM	Post-exertional malaise
POST	Follow-up test
PRE	Baseline test
PROM	Patient-reported outcome measures

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RPE	Rate of perceived exertion
SARS-CoV-2	Severe acute respiratory syndrome coronavirus type 2
SF-12	Short form 12 survey

Since its emergence in 2019, the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has been having an enormous global effect on health and wellbeing. Even though most individuals infected with SARS-CoV-2 will recover fully, there is a substantial proportion of people that have persistent or new symptoms weeks or months post infection[1,2]. These sequelae of a SARS-CoV-2 infection have been described with the term "long COVID" for the first time by patient groups online[3]. Several other names (e. g. post-acute sequelae of COVID-19, post-COVID syndrome) and definitions have been proposed to describe these persisting symptoms[4,5]. The World Health Organization has defined the Post COVID-19 condition (PCC) as symptoms without any other medical explanation that continue or develop after 3 months of the infection and persist for of at least 2 months[6,7].

With over 200 symptoms observed in PCC, there is a large heterogeneity in the clinical presentation of this new disease. However, one of the most common as well as debilitating symptoms is fatigue[8]. A German cohort study found that 21% of individuals with a positive test for SARS-CoV-2 showed clinically relevant fatigue levels at a median time of 9 months post infection[9]. The dominant role of fatigue within the PCC symptom cluster is demonstrated in a Dutch cohort, where 75.9% of PCC patients reported fatigue 3–6 months after the infection[10]. According to a meta-analysis by O'Mahoney et al.[11], fatigue affects 25.2% of individuals across hospitalized and non-hospitalized COVID-19 patients. There is vast evidence for the high burden of disease in PCC. Fatigue, reduced physical capacity, neurocognitive impairments as well as other symptoms negatively affect health-related quality of life and overall well-being[12–18]. Patients often display low muscular strength[19,20].and reduced endurance capacity[21]. Physical performance parameters are meaningful clinical outcomes in PCC as they are related to overall disease severity[12,14,19,20]. In terms of diagnosis, many impairments such as fatigue and reduced health-related quality of life (HRQoL) can be quantified using standardized questionnaires[12,21]. Besides these patient reported outcome measures, measuring handgrip strength has been shown to be a practical and valid tool to assess objective fatiguability[20,22].

To date, the pathophysiological pathways of acute infection, biological damage or dysregulation and PCC symptoms are not established. Hypotheses regarding the underlying mechanisms focus on damage to various tissues (e. g. heart, brain, mitochondria, endothelia) that are a direct consequence of viral infiltration and lead to a persistent dysregulation as well as ongoing systemic responses (e. g. dysautonomia, inflammation, autoimmunity, virus reactivation) in the aftermath of the acute viral infection[23–28].

A recent meta-analysis by Fernandez-de-Las-Peñas et al.[29] found that two years post infection, 28% of PCC patients still suffered from fatigue. These data emphasize the long-term trajectory PCC has in many individuals. A certain proportion of those who experience long-term PCC fatigue will meet the diagnostic criteria for myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS), which is a post-infectious syndrome that shares several clinical features with PCC[30]. One of the hallmark symptoms that is used to diagnose ME/CFS is post-exertional malaise (PEM). PEM is the worsening of symptoms typically 12–48 h after a strenuous physical, psychological or emotional task and can severely impair the ability to perform tasks of daily living[31]. In these cases, physical training according to common recommendations is contraindicated[32]. Using the DePaul Symptom Questionnaire-PEM (DSQ-PEM), which is a standard diagnostic tool to assess PEM, a high prevalence of PEM (58.7%) has been observed in an online survey with 213 participants who reported to be affected by long COVID symptoms[33].

To date, there are no curative therapies for PCC or ME/CFS and therapeutic approaches are mainly targeted towards symptom management[30]. Based on the positive effects physical activity has in many other chronic diseases, exercise has been proposed as a potential therapy in PCC for symptom relieve[32,34]. The positive effects of exercise on quality of life, fatigue and functional capacity in PCC have been shown in several interventional studies[35–40]. Furthermore, there is evidence for the overall safety of exercise programs in PCC[41,42]. Despite these promising results, Gloeckl et al. found that many exercise trials fail to address the management of PEM in PCC[43]. Based on practical experience, they suggest using the DSQ-PEM to screen for PEM and to apply an individualized and symptom-titration exercise regimen in those who show no or mild PEM to avoid symptom exacerbation. There are several other authors and institutions who propose a symptom-titrated exercise approach to account for PEM in PCC[32,34,43–45]. However, feasible symptom-titrated exercise programs that can be offered nearby patients' homes are still missing.

Therefore, in the present study, a multi-centre randomized controlled trial (RCT) was conducted to analyse the effectiveness of a symptom-titrated and individualized exercise program. It was hypothesized that a symptom-titrated exercise program in a real-world setting generates significant positive effects on (a) fatigue as a primary outcome, (b) health-related quality of life, (c) PEM and (d) physical performance parameters of hand grip strength and endurance capacity as secondary outcomes, compared with a wait-list control group.

Methods

Participants and study design

The RCT was conducted as a multi-centre study, i.e., the implementation of the training intervention and data collection took place in 19 selected fitness and health facilities in Germany (federal state Saarland, real-world setting) between April and December 2023. Primary and secondary outcomes were assessed at baseline (PRE) and after a ten-week period (POST), of which two weeks served as training familiarization and 8 weeks as exercise intervention. The study was approved by the ethics committee of the Medical Association responsible (identification number 07/23) and was conducted in accordance with the Declaration of Helsinki[46]. It was registered in the German Clinical Trials Register (ID: DRKS00031634) a priori. All participants gave written informed consent before participating in the study.

Participants were recruited via public media (newspaper, radio and social media). Furthermore, the general practitioners' association and the statutory health insurance fund provided information about the study to their patients. Interested individuals were able to enrol through a designated website where they also found detailed information about the study. They were subsequently sent an online questionnaire to screen for inclusion and exclusion criteria as well as to obtain sociodemographic data. Inclusion criteria were (a) age between 18 and 79 years, (b) confirmed SARS-CoV-2 infection (positive PCR test) $\geq$ 12 weeks before, (c) mild to moderate course of COVID-19, (d) presence of fatigue symptoms for $\geq$ 12 weeks, (e) < 1 h/week of physical exercise within the last 3 months, (f) no contraindications for physical training (pre-existing conditions, medication) and (g) a medical certificate for physical activity readiness. Exclusion criteria were a Post-COVID-19 Functional Status (PCFS)-score of 4 as this indicates an inability to perform activities of daily living and thus exercise without assistance[47] and hospitalization due to COVID-19.

Eligible individuals were allocated to the training facility closest to their place of residency. They were randomized to either the control (CON) or intervention (INT) group using stratification. Stratified randomisation is a variant of randomisation in which the participants are divided into subgroups based on important characteristics, which in this case were age and gender. This is intended to ensure that characteristics with particularly strong significance for the intervention are distributed equally across the study groups. Participants in CON were able to perform the same intervention after the follow-up test and were encouraged to maintain their lifestyle habits during the waiting period. The medical certificate for physical activity readiness had to be provided before the intervention began. Participants received information about their allocated group after the PRE diagnostics.

Training facilities

A multi-centre approach was chosen to achieve high external validity by recruiting a diverse sample from different locations and by choosing a non-laboratory setting for the intervention. The research sites were commercial fitness and health facilities located in the Saarland, Germany. Training facilities were recruited by using a convenience sample throughout the federal state. Subsequently, several steps were taken to ensure a high degree of study standardization and internal validity. It was ensured that the necessary equipment for testing and training interventions was available in all facilities. All trainers employed at the facilities and involved in the supervision of participants, data collection and intervention were exercise specialists with a completed or near-completed academic degree in exercise science or a related field. Before the start of the intervention, extensive training on study implementation and the test instruments was carried out in the participating facilities to ensure compliance with the study protocol and the standardised methodology. The facilities were regularly contacted and visited by the authors during data collection to ensure that all procedures were in line with the study protocol. For each participant, financial compensation was paid to the facilities, approximately equal to the industry standard membership fee.

Outcomes

The primary outcome of the study was the change in the fatigue severity scale (FSS) from PRE to POST. Secondary outcome measures were changes in health-related quality of life measured by SF-12, PEM using the DePaul Symptom Questionnaire and physical performance parameters of strength (hand grip strength, objective fatigability) and endurance capacity (Chester Step Test). Data were obtained digitally using online surveys. This approach permitted the straightforward collection of data in the training facilities and the centralized storage and subsequent data analysis. The data acquisition procedure for PRE and POST is shown in Fig. 1. The patient-reported outcome measures (PROMs) were recorded digitally at the beginning of a testing session, followed by the measurement of hand grip strength parameters using a specific protocol and endurance capacity using the Chester Step Test.

Patient reported outcome measures

The severity of perceived fatigability was assessed using the fatigue severity scale (FSS)[48–50]. The score represents the mean of nine items ranging from 1 to 7, with 7 being the highest degree of fatigue and values $\geq$ 4 indicating clinically relevant fatigue. The FSS has been used as a measure for patient-reported fatigue in PCC and is validated for this population[21].

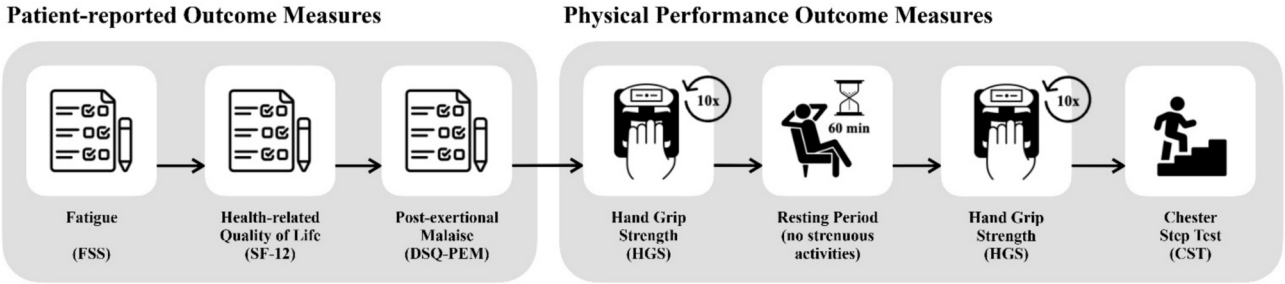

Fig. 1. Examination procedure.

In order to assess the influence of individualized exercise on HRQoL, the SF-12 questionnaire was used which is a validated tool with 12 questions for the general assessment of people's physical and mental health status[51]. The SF-12 comprises the areas of physical functioning, physical limitations, physical pain, general health, energy/fatigue, social functioning, emotional limitations and mental health, from which the sum scores for the mental component score (MCS) and a physical component score (PCS) are calculated[52]. Higher values for both scores are associated with a better state of health, lower values indicate a poorer state of health.

PEM was assessed by the German version of the DePaul Symptom Questionnaire Post-Exertional Malaise (DSQ-PEM[53]; German version[54]), which could be used as a valid tool in the German translation in previous studies[55]. Participants rated frequency and severity of each of five items on a scale of 0 to 4. The screening for PEM was positive when frequency and severity for at least one item was ≥ 2. For the total value of PEM, the mean of frequency and intensity of all items was calculated.

Hand grip strength

To determine strength and objective fatigability, a repetitive measurement of hand grip strength (HGS) was carried out using a hand dynamometer (EH101, Camry). The measurement procedure has been implemented by other authors before to determine HGS and objective fatigability in PCC and ME/CFS[20,22]. In this test, hand grip strength is measured 10 times in two series of measurements, one hour rest in between, using a hand dynamometer. The HGS of PCC patients decreases significantly after one hour in the second series of measurements[20]. Furthermore, the maximum hand grip strength (HGS, F_{max}) and the mean hand grip strength (F_{mean}) were determined. The decrease in strength within each series is represented by the fatigue ratio (F_{max}/F_{mean}) and the decrease between the two series by the recovery ratio (F_{mean1}/F_{mean2}).

Chester step test

The Chester Step Test (CST) is a submaximal multi-stage test and was used to investigate endurance capacity[56]. Participants step up and down on a 20 cm-high step at a rate of 15 steps per minute in the first stage. The step rate increased every 2 min by 10 steps/min and participants were guided by an acoustic metronome. Heart rate (HR) and rate of perceived exertion (RPE) were taken after each 2 min-stage. HR was measured by optical measurement with a wrist-worn device (vivosmart 5, Garmin, USA) and RPE with the Borg scale. The maximum number of stages was five and the test was terminated as soon as individuals failed to maintain the step rate, exceeded 80% of their estimated maximum HR (Equation 220—age) or reached an RPE of 15. The test result was the number of total steps at test termination. The CST is a reliable tool to asses endurance capacity in PCC[57] and can be administered to heterogenous groups with minimal space and material requirements. Furthermore, many activities of daily living (e. g. climbing stairs) are relatable to the task tested in the CST.

Training intervention

The training intervention consisted of individualized and symptom-titrated concurrent resistance and aerobic training over eight weeks plus a two-week familiarization period before the intervention. The guideline of the German Respiratory Society presented the framework for the volume and frequency of training in our study[34]. Figure 2 outlines the individual components of the study design.

Following the PRE diagnostic, participants in INT underwent a two-week familiarization phase in which they completed three supervised training sessions, before they began the actual eight-week training intervention. The training intervention was designed with the intention of providing a structured and effective training program while acknowledging the need for pacing strategies in people with PCC[58,59] to avoid over exertion and symptom exacerbation. Supervised sessions served to familiarize the participants with the individualized and symptom-titrated training as well as the training equipment. During these sessions, the exercise specialists guided the individuals in finding the appropriate training intensities and volumes in line with our training program. Before each session, the acute level of fatigue was assessed by answering the first item of the Brief Fatigue Inventory (BFI)[60]. Based on their fatigue severity, participants received a symptom-titrated training recommendation (see Table 1). By adjusting volume, intensity and intra-set breaks, the dose of training was adapted to the severity of the acute fatigue. Rather than using standardized intensities based on maximum values (e. g. one repetition maximum, maximum heart rate), an individualized approach was chosen. Intensities were determined using the OMNI-Scale as a measure of perceived exertion[61,62]. Furthermore, the exercise specialists instructed the patients to monitor symptoms after each session and modify the subsequent session if they perceived any worsening of overall well-being. In addition, participants were specifically advised to adjust the training program, if necessary, at any point, based on their own perception. Individualisation was achieved through

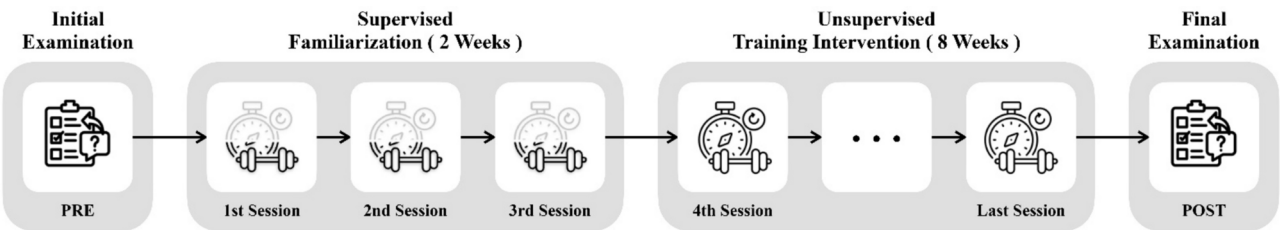

Fig. 2. Intervention procedure.

BFI	Fatigue severity	Load modification Resistance training	Load modification Endurance training
9–10	Maximum	Training is contraindicated	Training is contraindicated
6–8	High	2 training sets per exercise with 3 clusters of 4 repetitions each (10 s intra-set break)	Duration: 5–10 min Intensity: 4–6 RPE scale
3–5	Moderate	1st training set per exercise: 12 repetitions in a row 2nd training set per exercise: three clusters of 4 repetitions each (10 s intra-set break)	Duration: > 10 and ≤ 20 min Intensity: 4–8 RPE scale
0–2	Low	2 training sets per exercise with 12 repetitions in a row	Duration: > 20 and ≤ 30 min Intensity: 4–8 RPE scale

Table 1. Load modification depending on the brief fatigue index.

the training recommendations based on acute fatigue levels (see Table 1) and by enabling the participants to further auto-regulate the training parameters. The training sessions in the familiarization phase were supervised. In the following intervention phase, the participants trained without constant supervision. However, exercise specialists were always present in the facilities and could be consulted every time during training. After 4 weeks of training, participants consulted with the training staff to check training execution and discuss any exercise-related issue. Rather than attempting a progressive increase in training dose, participants were instructed to aim for regularity of training frequency while avoiding worsening of symptoms. The recommended training frequency was 1–3 sessions per week. Additional comments on the exercise prescription are presented in the supplementary materials.

Resistance and endurance training

Resistance training was performed on machines and was designed as a whole-body workout with the following exercises: (1) leg press, (2) leg extensions, (3) leg flexion, (4) latissimus pulldown, (5) seated rowing, (6) chest press, (7) back extensions and (8) abdominal press.

During the familiarization phase, training weights corresponding to a submaximal intensity of 8 on the 10-point OMNI-Scale were determined together with the exercise specialist. This weight was set to be the maximum weight participants should use for the first 4 weeks. Participants performed two sets of twelve repetitions. The rest period between sets was 90–120 s. To account for fatigue fluctuation, the set structure was modified by implementing intra-set breaks (see Table 1). Dividing sets in clusters with short rest periods between each cluster has shown to be an effective strategy to attenuate parameters of exercise-induced fatigue while ensuring effective training stimuli[63,64]. It has also been applied successfully in cardiac patients with low exercise tolerance[65]. Additionally, participants were instructed to further alter the training load (e.g. reduce training weights) if necessary. Exercise intensity was determined based on RPE as perceived exertion integrates a wide array of neurophysiological perceptions[66] and is therefore a meaningful metric to account for different fatigue levels in PCC.

Consequently, the OMNI scale was used to control the intensity of endurance training. The training dose was adjusted by modifying intensity as well as duration (see Table 1). Regarding the choice of exercise form, participants could choose freely from the ergometers available in the facility. This was intended to consider personal preferences and thus achieve the highest possible compliance in endurance training.

Statistical analysis

To examine the differences over time and between the two groups, we ran mixed models. For each dependent variable, group (CON vs. INT) and time as fixed effects were added. Furthermore, the interaction of group and time was added. In addition, random intercepts for the individual participants were estimated. Including the different training facilities as another (third) level resulted in a variance of the random intercept close to zero. Thus, there was no substantial variance that could be contributed to the training facilities; therefore, this level was removed from the analysis. Following the recommendations by Shatz[67], assumptions for mixed models were visually inspected. Most of the analysis were deemed to be sufficiently satisfied. If we saw any issues in model assumptions, we checked whether exclusion of outlying cases and data transformation techniques yielded similar results. As this were the case, we report only the original results.

All individuals with at least one data point at both PRE and POST were included in the intention-to-treat analysis, regardless of the number of actual training sessions. Participants with missing data points were included in the analysis as linear mixed models are a recommended procedure for the analysis of incomplete data[68].

For a moderator analysis, we used the same analysis but included only the intervention group (thus dropping the group term) and added the moderator. For easier interpretation, the moderators were centred around the mean. We tested for quadratic relationships between the moderator and the intervention effect; however we found none in all our moderator analysis. Thus, we kept only a linear relationship to simplify interpretation and reporting. In this analysis, we determined whether the time variable interacted with the moderator. To this end, we used a linear mixed model with individual participants as random intercepts. Time, the moderator and their interaction were included as fixed effects. The absolute number of training sessions in the intervention period as well as the PCFS score, and gender were included as variables. In Table 3, data are presented as means ± standard deviation, the delta values were calculated as POST–PRE values.

The R software environment (Version 4.3.3) was used for the intention-to-treat data analysis. Mixed models were estimated using the lme4 package (Version 1.1.35.1) and the easystats ecosystem was used for report generation[69]. Due to the exploratory nature of our study and the small number of published studies at

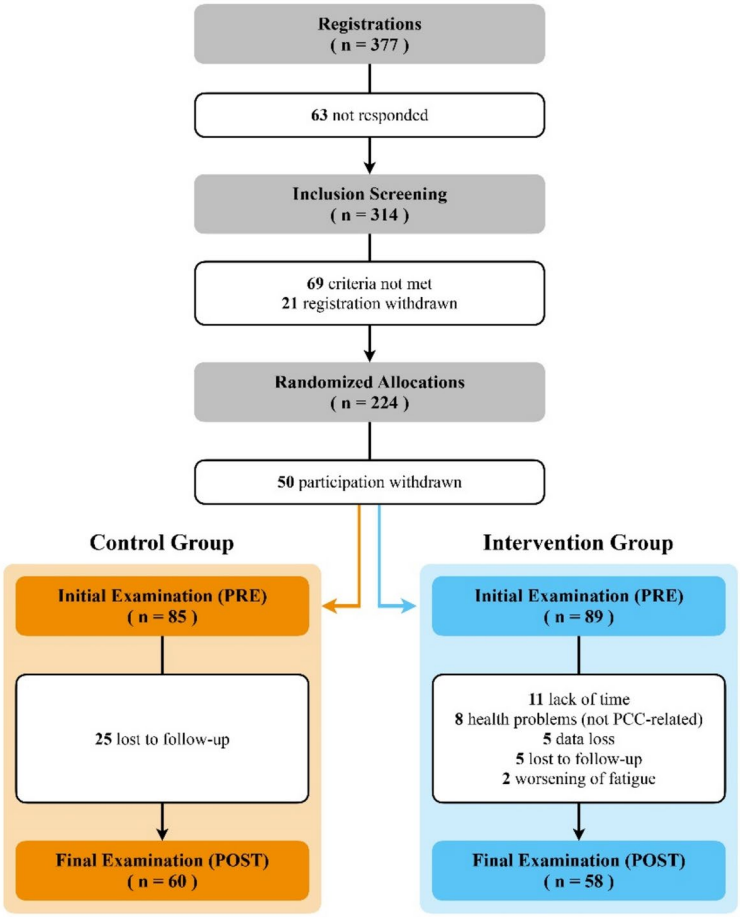

Fig. 3. Flow of participants.

Anthropometric data	Total n = 118 (male = 37; female = 81)	CON n = 60 (male = 17; female = 43)	INT n = 58 (male = 20; female = 38)
Age [years]	53.5 ± 11.9	53.5 ± 12.3	52.8 ± 11.6
Height [cm]	170.0 ± 8.6	169.7 ± 8.7	170.3 ± 8.6
Bodyweight [kg]	78.9 ± 19.3	78.0 ± 20.0	79.9 ± 18.6
BMI [kg/m^2]	27.1 ± 5.2	26.8 ± 4.9	27.4 ± 5.4

Table 2. Descriptive data of participants. n = quantity, *CON* control group, *INT* intervention group, *cm* centimetre, *kg* kilogram, *BMI* body mass index, m^2 square metres, none of the anthropometric variables differed between groups at baseline (all $p > 0.05$).

study conceptualization, we did not perform an a priori sample size calculation or power analysis. Instead, we integrated all interested participants who wanted to take part in the study and fulfilled the inclusion criteria. We deemed all effects with a p-value < 0.05 as significant.

Results

A participant flow chart is given in Fig. 3. Between study inclusion and PRE, 50 participants who were randomized did not commence the study. Additionally, 56 participants (CON: 25; INT: 31) ceased participation between PRE and POST.

Table 2 shows the anthropometric data of the participants. A total of 174 people were randomized of which 118 were included in the final analysis. There were no significant group differences at the beginning of the study. During the familiarization and training phase, participants of INT performed 19.9 ± 5.7 sessions with a total duration of the intervention of 9.7 ± 3.1 weeks.

Main outcomes

The descriptive values of the parameters at PRE and POST as well as the changes are illustrated in Table 3. The baseline data did not differ significantly between groups. Due to technical input errors during digital data transmission, single individual values could not be included in the analysis. For the sake of completeness, the number of missing values for each variable and group is given in square brackets after the mean ± standard deviation data.

Compared to CON, the intervention group had a significant favourable change as indicated by the mixed models in FSS (b = −0.93, 95% [−1.30,−0.56], $p < 0.001$), F_{mean} (b = 2.68, 95% [0.93,4.43], $p = 0.003$), F_{max} (b = 3.02, 95% [0.78,5.26], $p = 0.008$), SF-12 mental score (b = 3.91, 95% [0.37,7.44], $p = 0.031$), SF-12 physical score (b = 3.62, 95% [0.63,6.61], $p = 0.018$) and the total steps of CST (b = 27.13, 95% [4.28,49.99], $p = 0.020$). There was no statistical difference between the groups in the fatigue ratios as well as the recovery ratio.

The DSQ-PEM indicated PEM in all participants in CON at study onset. In INT, two participants were below the threshold for PEM at PRE. Mean PEM frequency and intensity showed overall mild to moderate PEM in CON (PEM: 2.39 ± 0.68) and INT (PEM: 2.43 ± 0.75) at study onset.

The covariates used for interaction analysis were the number of training sessions, PCFS score and gender. We found a linear relationship between time and the moderator such as individuals with more training sessions had an increased decline of FSS (b = −0.07, 95% [−0.12,−0.02], $p = 0.009$), increased rise of F_{mean} (b = 0.25, 95% [0.09,0.40], $p = 0.002$), increased rise of F_{max} (b = 0.26, 95% [0.10,0.41], $p = 0.002$) and an increased decline of PEM b = −0.04, 95% [−0.07,0.00], $p = 0.024$). There were no effects of the PCFS score as well as gender on the outcome parameters.

Discussion

The purpose of this study was to investigate the effects of an individualized, symptom-titrated and feasible exercise program on fatigue, health related quality of life, The exercise program had a significant effect on fatigue in comparison to the control group but not on objective fatigability. Furthermore, the intervention had a significant effect on handgrip strength, endurance capacity and HRQoL. There were no effects on PEM as well as measures of objective fatigability.

Fatigue and fatigability

The individualized and symptom-titrated exercise program significantly reduced fatigue in INT from 5.67 to 4.51 compared to CON (Pre: 5.49; Post: 5.29) on the FSS. These findings are in line with Jimeno-Almazán et al. who found mean improvements on the FSS from 5.0 to 3.4 after eight weeks of supervised concurrent training[38]. The decrease of fatigue in INT (−1.14; 20.1%) is within the range of the minimal clinically important difference for a global change (0.5 to 1.2)[70]. In contrast to our study, Jimeno-Almazán et al. determined endurance training intensities based on objective parameters (e.g. heart rate reserve) and used RPE in those individuals who could not adhere to objective parameters. Kerling et al.[35] did not find greater improvements in fatigue than in a control group after a three month exercise intervention. Exercise intensities were based on maximum heart rate (60–75%) and the designated training volume was not individually adjusted but set at 150 min per week, with additional bouts of intense exercise. The authors noted that they overestimated the participants'

Outcome parameter	Group	PRE	POST	Delta POST–PRE	Cohen's *d* [95% CI]	Mixed linear model Time × Group
FSS [score]	CON INT	5.49 ± 0.87 [0] 5.67 ± 0.92 [1]	5.29 ± 1.07 [2] 4.51 ± 1.42 [1]	−0.23 ± 0.82 −1.14 ± 1.19	− 0.23 [−0.02, −0.44] −0.89 [−0.60, −1.18]	$p < 0.001$
SF-12 MCS [score]	CON INT	39.95 ± 10.4 [0] 41.62 ± 10.89 [1]	42.08 ± 10.86 [2] 47.86 ± 10.15 [1]	2.18 ± 8.57 5.94 ± 10.57	0.20 [0,41, 0.00] 0.55 [0.83, 0.28]	$p = 0.031$
SF-12 PCS [score]	CON INT	34.79 ± 7.88 [0] 34.42 ± 8.85 [1]	35.31 ± 9.72 [2] 38.75 ± 10.91 [1]	0.81 ± 6.23 4.33 ± 9.71	0.09 [0.26, −0.09] 0.42 [0.68, 0.16]	$p = 0.018$
PEM [mean]	CON INT	2.39 ± 0.68 [0] 2.43 ± 0.75 [1]	2.23 ± 0.76 [2] 2.02 ± 0.85 [1]	−0.19 ± 0.65 −0.41 ± 0.69	−0.26 [0.02, −0.49] −0.50 [−0.27, −0.73]	$p = 0.065$
F_{max} [kg]	CON INT	29.10 ± 13.35 [0] 30.23 ± 10.37 [0]	27.54 ± 11.48 [0] 31.74 ± 11.45 [2]	−1.56 ± 7.85 1.45 ± 3.43	−0.12 [0.03, −0.28] 0.13 [0.20, 0.05]	$p = 0.008$
F_{mean} [kg]	CON INT	23.09 ± 11.05 [0] 24.59 ± 9.59 [0]	22.39 ± 10.39 [0] 26.69 ± 10.07 [2]	−0.70 ± 5.78 1.97 ± 3.40	−0.06 [0.07, −0.20] 0.19 [0.28, 0.11]	$p = 0.003$
Fatigue ratio 1 [Index]	CON INT	1.22 ± 0.16 [0] 1.18 ± 0.11 [0]	1.21 ± 0.17 [1] 1.15 ± 0.08 [5]	−0.01 ± 0.14 −0.04 ± 0.12	−0.05 [0.17, −0.27] −0.38 [−0.01,− 0.74]	p = .276
Fatigue ratio 2 [Index]	CON INT	1.19 ± 0.17 [2] 1.19 ± 0.13 [2]	1.21 ± 0.15 [2] 1.15 ± 0.08 [2]	0.01 ± 0.18 −0.04 ± 0.11	0.04 [0.32, −0.24] −0.32 [−0.05, −0.59]	$p = 0.085$
Recovery ratio [Index]	CON INT	0.96 ± 0.17 [2] 0.98 ± 0.12 [2]	0.95 ± 0.12 [3] 1.00 ± 0.12 [5]	−0.01 ± 0.16 0.03 ± 0.14	−0.09 [0.18, −0.36] 0.26 [0.61, −0.08]	$p = 0.191$
CST Total Steps [number]	CON INT	166.40 ± 76.04 [0] 159.42 ± 75.72 [1]	161.42 ± 76.54 [1] 183.22 ± 71.21 [4]	−3.56 ± 58.70 22.72 ± 65.18	−0.05 [0.15, −0.24] 0.30 [0.54, 0.07]	$p = 0.020$

Table 3. Changes in main outcome measures as means ± standard deviation. *CON* control group, *INT* intervention group, *FSS* fatigue severity scale, *SF-12* short-form 12, *MCS* mental component score, *PCS* physical component score, *CST* chester step test; number in square brackets delineates number of missing values.

ability to adhere to their program and concluded that only patients with milder forms of fatigue could benefit from their program. Given these results, the data presented here underline the importance of an individualized and symptom-titrated approach to exercise therapy in PCC[32,43,71]. Instructing patients to autoregulate training has already been applied as an effective strategy to account for symptom fluctuation in other studies[42]. To the authors' knowledge, this is the first RCT to investigate the efficacy of exercise as a stand-alone therapy to reduce fatigue in PCC, with exercise prescriptions based on daily fatigue levels and exercise intensity determined by RPE rather than objective parameters. Furthermore, the findings show that using cluster sets in resistance training is a feasible strategy in PCC as the additional intra-set breaks ameliorate perceptual, mechanical and metabolic fatigue[63]. Regarding the descriptive values (no statistical significance), a reduction in PEM was observed in the intervention group, which confirms the benefit of symptom-titrated exercise for moderate PEM in PCC patients.

We observed no changes in objective fatigability as assessed by fatigue ratios as well as recovery ratio in either group. When analysing patient reported fatigue by questionnaire and objective fatigability by an isokinetic fatigue task, Fietsam et al. found that patients with PCC had increased fatigue but not fatigability compared to a control group[72]. This is contrasted by other observational studies that assessed objective fatigability with the same repeated HGS protocol as in this study and found high levels of subjective fatigue as well as objective fatigability in ME-CFS and PCC[20,22]. To our knowledge, this is the first experimental study to investigate changes in fatigue as well as objective fatiguability after an exercise intervention in PCC. In a cohort of PCC patients, Legler et al. observed improvements in fatigue ratios at two follow-ups at 3–8 months and 17–20 months after COVID-19 manifestation[73]. While exercise in our study has reduced the subjective fatigability during activities of daily living as evidenced by the reduction in FSS scores, it did not improve the objective fatigability (fatigue ratio1/2, recovery ratio) in tasks requiring consecutive maximum exertion of effort such as the repeated HGS test. Our findings also allude to deconditioning not being the cause for objective fatigability in PCC. Given the increase of maximum (1.45 ± 3.43 kg) and mean strength (1.97 ± 3.40 kg) in INT, muscular fatigability is likely not an effect of a lack of overall strength. These are relevant results as they point towards different neurobiological mechanisms for subjective and objective fatigability in PCC. As other authors have stated before, investigating these distinct pathways in fatigue is of paramount importance to provide a basis for targeted therapeutical interventions[50,74–77]. Given the evidence on the multidimensional nature of (chronic) fatigue symptoms, it is apparent that research in PCC so far often focuses solely on self-reported fatigue and neglects objective fatigability measures such as repeated hand grip strength tests. Furthermore, analysing biomarkers (e.g. neurophysiological measurements) in addition to functional assessment of fatigability has the potential to shine light on the neurobiological etiology of fatigue in PCC[78]. It should be noted that, while repeated HGS has been used as a measure of objective fatigability in PCC and ME/CFS before[20,22,73], there is currently no consensus on a definition for objective fatigability and several instruments have been proposed for its evaluation[74,76].

Health-related quality of life

The exercise intervention led to significant improvements in the mental component as well as the physical component of the SF-12. Lower levels of HRQoL are a consequence of the wide array of symptoms in PCC[11,79] and are associated with pain and discomfort in PCC patients[80]. Furthermore, HRQoL has found to worsen with fatigue severity[14]. Symptoms experienced during the acute phase of infection lead to a decrease in HRQoL that is typically no longer present after three months in SARS-CoV-2 survivors without PCC[81]. In a German cohort of 318 PCC patients, the results in SF-36 (longer version of SF-12) were 36.3 ± 10.1 for the PCS and 40.9 ± 11.6 MCS[79]. At POST the results in INT (PCS: 38.75 ± 10.91; MCS: 47.86 ± 10.15) were still below the German standard values (PCS: 48.4 ± 9.4; MCS: 50.9 ± 8.8)[79] for the physical health score while having normalized for mental health. These results have a strong implication on patients' overall wellbeing as HRQoL was found to be correlated with perceived ability to work in PCC[79]. While many different biological abnormalities were observed, there is still an absence of objective diagnostic biomarkers in PCC[30]. In addition, many PCC symptoms also occur in the general population or other diseases, so their presence is not necessarily a consequence of a SARS-CoV-2 infection sequelae[82,83]. HRQoL is therefore a meaningful outcome, as it reflects the extent to which individuals meeting the WHO definition for PCC suffer from their disease.

Our results proof that an individualized and symptom-titrated exercise program is effective in improving HRQoL and the overall burden of disease. The observed effects are in line with other studies investigating the effects of physical rehabilitations (e.g. exercise therapy) on HRQoL in PCC[84].

Physical performance

The exercise intervention led to significant changes in parameters of physical performance. The changes in maximum and mean HGS were significantly greater in INC than CON. Furthermore, participants in INC showed significantly greater improvements in the number of steps during the CST, indicating a higher endurance capacity in submaximal tasks of daily living (e.g. climbing stairs). Deterioration in physical performance and muscular weakness in particular are common observations in PCC[85]. According to data from a representative German cohort, mean HGS is 32.2 ± 5.9 kg for females aged 50–54 and 49.1 ± 8.5 kg for males aged 55–59 in the healthy reference population[86]. In our study, at PRE mean HGS was 19.04 ± 6.03 kg for females (age 51 ± 12 year) and 34.31 ± 10.12 kg for males (age 57 ± 11 years). These are compelling findings as HGS is associated with overall functional capacity in PCC[19]. Furthermore, low HGS predicts the onset of several other chronic diseases (e.g. type 2 diabetes, cardiovascular disease) and overall mortality[87]. The improvements in HGS indicate the efficacy of the resistance training intervention and point to exercise-induced functional and structural adaptions on the peripheral level.

Several potential pathophysiological processes may result in muscular weakness and loss of functional capacity in PCC. It is well established that SARS-CoV-2 infiltration can give rise to a pronounced inflammatory response, which in turn can cause alterations in muscle structure, mitochondrial dysfunction, and endothelial

damage. This can result in a reduction in muscle mass and physical performance[88,89]. Persistent systemic inflammation beyond the acute phase of disease has been proposed as a pathomechanism in PCC[30] and can negatively impact muscle protein metabolism as well as functional capacity[88,90]. Castro et al.[91] have identified elevated inflammatory markers accompanied with reduced functional capacity in patients with PCC in comparison to a control group. Another area of interest in the search for causative mechanisms is the potential role of mitochondrial dysfunction as a result of viral infiltration[26,92,93]. Studies have identified myopathic changes affecting muscle structure, mitochondrial functioning and endothelia that are directly associated with reduced strength and performance[93–98]. It is plausible that peripheral changes not only yield a deterioration in physical performance but also play a causative role in the development of PCC fatigue and PEM[96–98].

Given the extensive research conducted within the field of sports medicine on the biological abnormalities commonly observed in several chronic diseases, there is a wealth of evidence for the beneficial effects of exercise on mitochondrial functioning, inflammation, metabolism and other biological pathways potentially relevant in PCC[99–103]. Despite the current paucity of consensus on the pathophysiology, the available evidence suggests that exercise may act as a therapeutic agent in PCC by addressing the underlying pathomechanisms rather than merely alleviating symptoms and counteracting deconditioning. Although we did not assess biological markers (e.g. laboratory markers, muscle biopsy), the improvements in physical performance and HRQoL as well as the reduction of fatigue observed in our study nevertheless provide support for this hypothesis. Based on the growing body of research on the effectiveness of exercise, further research is encouraged to elucidate exercise-induced biological changes and their link to PCC pathophysiology.

Safety and feasibility

The present study shows that an individualized and symptom-titrated exercise program is safe and feasible in people with PCC without worsening the fatigue severity. Between PRE and POST 32.2% of all participants (CON: 29.4%; INT: 34.8%) ceased the intervention. The most prevalent reasons for discontinuation in INT were lack of time (n = 11; 12.4%) and health problems that were not related to PCC (n = 8; 9.0%). Kerling et al. were able to include 66% of the participants that were allocated to their 3-month exercise intervention in their final analysis[35]. Jimeno-Almazán reported a lower rate of discontinuation (7.0%) in PCC patients performing concurrent training[36]. A possible explanation for this variation is that all sessions were supervised in the latter study which potentially has a positive effect on adherence. In the present study, two participants discontinued the exercise intervention due to transient worsening of fatigue. They ceased participation after the third and sixth training session, respectively. In one participant it was possible to measure fatigue severity by FSS three weeks after the last training session and we found no clinically relevant difference to study onset (5.9 to 5.7). Other than that, no adverse events were recorded. Many triggers can cause symptom worsening in PCC[104] and it is plausible that transient increases in fatigue occurred in CON as well. While there are effective strategies (e.g. pacing) to reduce the risk for symptom exacerbation, PEM occurs even when pacing is applied[59]. It is important to note that pacing is a method of disease management, but not a therapeutic strategy in PCC and ME/CFS[58]. Therefore, pacing or energy management is a tool that should be combined with an exercise intervention as proposed by Gloeckl et al.[43]. Tryfonos et al. have recently shown that acute bouts of exercise did not lead to greater fatigue worsening in PCC with PEM symptoms than in healthy controls and concluded that a symptom-oriented exercise prescription can counteract the peripheral pathologies found in their participants[105]. While these are relevant findings, the question of a long-term or cumulative risk of exercise was still unanswered. The present study partially closes this knowledge gap by demonstrating a significant improvement in fatigue, physical capacity and HRQoL of PCC patients through a symptom-titrated training intervention over several weeks, without a parallel deterioration in the recorded PEM.

Within the scientific and patient community there is some controversy around the effectiveness and safety of graded exercise therapy in chronic fatigue syndromes[106,107]. For this reason, we want to highlight that an individualized and symptom-titrated exercise program as proposed by other authors[34,43,108] and applied in our study is a distinctively different approach. Rather than using fixed increments and objective markers for exercise prescription, we determined the training dose based on daily fatigue and instructed patients to further adjust volume and intensity if necessary. This approach considers symptom fluctuation and is an effective strategy for ensuring long-term and safe engagement in physical activity. Furthermore, given the interindividual variability in PEM, fatigue triggers and experience[104,109], it is essential to empower PCC patients to adjust their training autonomously while still providing structured guidance. The present findings contribute to the search for effective and safe exercise programs in PCC without a worsening of any symptoms. The use of acute daily fatigue as a reference point for exercise adjustment seems to be a feasible approach to prevent worsening of exercise-induced fatigue in PCC patients with moderate PEM levels. PEM is also a hallmark symptom of ME/CFS, and a significant proportion of patients with PCC will eventually meet the diagnostic criteria for ME/CFS[10,30]. Given the substantial clinical overlap between ME/CFS and PCC[110], we encourage future research to investigate the feasibility of an individualized and symptom-titrated exercise program in patients with ME/CFS who display a baseline functional capacity that allows them to engage in exercise.

This study shows that exercise therapy for PCC patients can be safely performed in commercial fitness and health facilities. With over 9,000 facilities in Germany, they play an important role for public health in providing preventive and rehabilitative exercise in an easy accessible, outpatient setting[111].

Strength and limitations

A strength of the present study was the inclusion of a wait-list control group and the multi-centre approach, with tests and training conducted in a real-life setting. Furthermore, a novel approach to individualized and symptom-titrated exercise was proposed which is of high relevance in clinical practices. To the authors knowledge this is

the first exercise trial investigating the effects of exercise on parameters of fatigue as well as objective fatigability in PCC.

While a relatively large number of participants was included in the study, the lack of an a priori sample size calculation should be addressed as a methodological limitation.

For the CST, a wrist-worn activity tracker with an optical heart rate sensor was used, which is not the gold standard for heart rate measurement. Detached from the control of the termination criteria, a more accurate heart rate measurement could provide a more detailed heart rate history, potentially supporting a more comprehensive evaluation and thus represents a limitation of this study. Furthermore, the digital data collection via mobile devices was a time and cost-efficient method for the multi-centre study but led to some instances of data loss when data were not correctly transmitted. Digital or analogue data backups that are stored at the research facilities are a possible way to deal with this issue in future studies. Although prescribing intensities based on subjective parameters has been shown to be effective and feasible, we did not record training intensities based on maximum values (e. g. one repetition maximum, maximum heart rate). This could help to determine objective measures for intensity prescription in PCC.

One major limitation of this study is the relatively high attrition rate. In particular, the number of individuals who did not commence the study despite being included or who dropped out of the intervention must be acknowledged. Possible reasons for non-participation or discontinuation might be a generally low expectancy of improvement or previous negative experiences with physical activity.

Conclusion

An individualized and symptom-titrated exercise program is effective in reducing fatigue as well as improving HRQoL and parameters of physical performance in PCC. A positive screening for PEM is not a contraindication for a structured exercise program that is tailored to daily fatigue in those individuals. Adjusting the training dose to the acute level of fatigue is a feasible strategy to ensure safe exercise in PCC patients with mild to moderate PEM. These findings underline the importance of exercise therapy in PCC and support the previous expert opinions and guidelines. This study indicates that commercial fitness and health facilities represent an appropriate setting for safe and effective outpatient exercise therapy. Future research is needed to elucidate how exercise-induced biological adaptations affect PCC pathophysiology.

Data availability

As participants did not consent to the use of their individual data by third parties, the dataset is not publicly available, but is available from the corresponding author on reasonable request.

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References

1. Thompson, E. J. et al. Long COVID burden and risk factors in 10 UK longitudinal studies and electronic health records. *Nat. Commun.* **13**, 3528 (2022).
2. Nguyen, K. H. et al. Prevalence and factors associated with long COVID symptoms among U.S. adults. *Vaccines* **12**, 99 (2024).
3. Callard, F. & Perego, E. How and why patients made Long Covid. *Soc. Sci. Med.* **268**, 113426 (2021).
4. Chaichana, U. et al. Definition of post-COVID-19 condition among published research studies. *JAMA Netw. Open* **6**, e235856 (2023).
5. Rando, H. M. et al. Challenges in defining Long COVID: Striking differences across literature, Electronic Health Records, and patient-reported information. *medRxiv* https://doi.org/10.1101/2021.03.20.21253896 (2021).
6. World Health Organization (WHO). Post COVID-19 condition (Long COVID). Available at https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition (2022).
7. Soriano, J. B., Murthy, S., Marshall, J. C., Relan, P. & Diaz, J. V. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect. Dis* **22**, e102–e107 (2022).
8. Gheorghita, R. et al. The knowns and unknowns of long COVID-19: From mechanisms to therapeutical approaches. *Front. Immunol.* **15**, 1344086 (2024).
9. Hartung, T. J. et al. Predictors of non-recovery from fatigue and cognitive deficits after COVID-19: A prospective, longitudinal, population-based study. *EClinicalMedicine* **69**, 102456 (2024).
10. Cornelissen, M. E. B. et al. Fatigue and symptom-based clusters in post COVID-19 patients: a multicentre, prospective, observational cohort study. *J. Transl. Med.* **22**, 191 (2024).
11. O'Mahoney, L. L. et al. The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. *EClinicalMedicine* **55**, 101762 (2023).
12. Vélez-Santamaría, R. et al. Functionality, physical activity, fatigue and quality of life in patients with acute COVID-19 and long COVID infection. *Sci. Rep.* **13**, 19907 (2023).
13. de Oliveira Almeida, K. et al. A systematic review on physical function, activities of daily living and health-related quality of life in COVID-19 survivors. *Chronic Illn.* **19**, 279–303 (2023).
14. Beyer, S. et al. Post-COVID-19 syndrome: Physical capacity, fatigue and quality of life. *PLoS ONE* **18**, e0292928 (2023).
15. Kim, Y., Bae, S., Chang, H.-H. & Kim, S.-W. Long COVID prevalence and impact on quality of life 2 years after acute COVID-19. *Sci. Rep.* **13**, 11207 (2023).
16. Malesevic, S. et al. Impaired health-related quality of life in long-COVID syndrome after mild to moderate COVID-19. *Sci. Rep.* **13**, 7717 (2023).
17. Yalçın-Çolak, N., Kader, Ç., Eren-Gök, Ş & Erbay, A. Long-term symptoms and quality of life in persons with COVID-19. *Infect. Dis. Clin. Microbiol.* **5**, 212–220 (2023).
18. Sanal-Hayes, N. E. M., Mclaughlin, M., Hayes, L. D., Berry, E. C. J. & Sculthorpe, N. F. Examining well-being and cognitive function in people with long Covid and ME/CFS, and age-matched healthy controls: A case-case-control study. *Am. J. Med.* https://doi.org/10.1016/j.amjmed.2024.04.041 (2024).
19. do Amaral, C. M. S. S. B. et al. Low handgrip strength is associated with worse functional outcomes in long COVID. *Sci. Rep.* **14**, 2049 (2024).

20. Paffrath, A. *et al. Repeated Hand Grip Strength is an Objective Marker for Disability and Severity of Key Symptoms in Post-COVID ME/CFS* (2024).
21. Naik, H. et al. Evaluating fatigue in patients recovering from COVID-19: Validation of the fatigue severity scale and single item screening questions. *Health Qual. Life Outcomes* **20**, 170 (2022).
22. Jäkel, B. et al. Hand grip strength and fatigability: Correlation with clinical parameters and diagnostic suitability in ME/CFS. *J. Transl. Med.* **19**, 159 (2021).
23. Najafi, M. B. & Javanmard, S. H. Post-COVID-19 syndrome mechanisms, prevention and management. *Int. J. Prev. Med.* **14**, 59 (2023).
24. Perumal, R. et al. Biological mechanisms underpinning the development of long COVID. *iScience* **26**, 106935 (2023).
25. Parotto, M. et al. Post-acute sequelae of COVID-19: Understanding and addressing the burden of multisystem manifestations. *Lancet Respir. Med.* **11**, 739–754 (2023).
26. Molnar, T. et al. Mitochondrial dysfunction in long COVID: Mechanisms, consequences, and potential therapeutic approaches. *GeroScience* https://doi.org/10.1007/s11357-024-01165-5 (2024).
27. Klein, J. et al. Distinguishing features of long COVID identified through immune profiling. *Nature* **623**, 139–148 (2023).
28. Kenny, G., Townsend, L., Savinelli, S. & Mallon, P. W. G. Long COVID: Clinical characteristics, proposed pathogenesis and potential therapeutic targets. *Front. Mol. Biosci.* **10**, 1157651 (2023).
29. Fernandez-de-Las-Peñas, C. et al. Persistence of post-COVID symptoms in the general population two years after SARS-CoV-2 infection: A systematic review and meta-analysis. *J. Infect.* **88**, 77–88 (2024).
30. Scheibenbogen, C. et al. Fighting post-COVID and ME/CFS - development of curative therapies. *Front. Med.* **10**, 1194754 (2023).
31. Mateo, L. J. et al. Post-exertional symptoms distinguish myalgic encephalomyelitis/chronic fatigue syndrome subjects from healthy controls. *Work (Reading, Mass)* **66**, 265–275 (2020).
32. World Physiotherapy. *Safe Rehabilitation Approaches for People Living with Long COVID. Physical Activity and Exercise* (World Physiotherapy, 2021).
33. Twomey, R. et al. Chronic fatigue and postexertional malaise in people living with long COVID: An observational study. *Phys. Therapy* https://doi.org/10.1093/ptj/pzac005 (2022).
34. German Respiratory Society. *S1-Leitlinie Long/ Post-COVID - Living Guideline* (2023).
35. Kerling, A. et al. Effects of a randomized-controlled and online-supported physical activity intervention on exercise capacity, fatigue and health related quality of life in patients with post-COVID-19 syndrome. *BMJ (Clinical Research ed.)* **16**, 33 (2024).
36. Jimeno-Almazán, A. et al. Effects of a concurrent training, respiratory muscle exercise, and self-management recommendations on recovery from post-COVID-19 conditions: The RECOVE trial. *J. Appl. Physiol.* **134**, 95–104 (2023).
37. Mooren, J. M. et al. Medical rehabilitation of patients with post-COVID-19 syndrome-A comparison of aerobic interval and continuous training. *J. Clin. Med.* **12**, 6739 (2023).
38. Jimeno-Almazán, A. et al. Rehabilitation for post-COVID-19 condition through a supervised exercise intervention: A randomized controlled trial. *Scand. J. Med. Sci. Sports* **32**, 1791–1801 (2022).
39. Oliveira, M. R., Hoffman, M., Jones, A. W., Holland, A. E. & Borghi-Silva, A. Effect of pulmonary rehabilitation on exercise capacity, dyspnea, fatigue, and peripheral muscle strength in patients with post-COVID-19 syndrome: A systematic review and meta-analysis. *Arch. Phys. Med. Rehabil.* https://doi.org/10.1016/j.apmr.2024.01.007 (2024).
40. Fernández-Lázaro, D., Santamaría, G., Sánchez-Serrano, N., Caeiro, E. L. & Seco-Calvo, J. Efficacy of therapeutic exercise in reversing decreased strength, impaired respiratory function, decreased physical fitness, and decreased quality of life caused by the post-COVID-19 syndrome. *Viruses* **14**(12), 2797. https://doi.org/10.3390/v14122797 (2022).
41. Kogel, A. et al. Physical exercise as a treatment for persisting symptoms post-COVID infection: Review of ongoing studies and prospective randomized controlled training study. *Clin. Res. Cardiol. Off. J. German Cardiac. Soc.* **112**, 1699–1709 (2023).
42. Sick, J. & König, D. Exercise training in non-hospitalized patients with post-COVID-19 syndrome—A narrative review. *Healthcare* **11**(16), 2277. https://doi.org/10.3390/healthcare11162277 (2023).
43. Gloeckl, R. et al. Practical recommendations for exercise training in patients with long COVID with or without post-exertional malaise: A best practice proposal. *Sports Med. Open* **10**, 47 (2024).
44. Jimeno-Almazán, A. et al. Post-COVID-19 syndrome and the potential benefits of exercise. *Int. J. Environ. Res. Public Health* **18**(10), 5329. https://doi.org/10.3390/ijerph18105329 (2021).
45. Colas, C. et al. Physical activity in long COVID: A comparative study of exercise rehabilitation benefits in patients with long COVID, coronary artery disease and fibromyalgia. *Int. J. Environ. Res. Public Health* **20**(15), 6513. https://doi.org/10.3390/ijerph20156513 (2023).
46. World Medical Association. Declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA* **310**, 2191–2194 (2013).
47. Klok, F. A. et al. The Post-COVID-19 Functional Status scale: A tool to measure functional status over time after COVID-19. *Eur. Respiratory J.* **56**(1), 2001494. https://doi.org/10.1183/13993003.01494-2020 (2020).
48. Krupp, L. B., LaRocca, N. G., Muir-Nash, J. & Steinberg, A. D. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch. Neurol.* **46**, 1121–1123 (1989).
49. Valko, P. O., Bassetti, C. L., Bloch, K. E., Held, U. & Baumann, C. R. Validation of the fatigue severity scale in a Swiss cohort. *Sleep* **31**, 1601–1607 (2008).
50. Enoka, R. M., Almuklass, A. M., Alenazy, M., Alvarez, E. & Duchateau, J. Distinguishing between fatigue and fatigability in multiple sclerosis. *Neurorehabilitation Neural Repair* **35**, 960–973 (2021).
51. Drixler, K., Morfeld, M., Glaesmer, H., Brähler, E. & Wirtz, M. A. Validierung der Messung gesundheitsbezogener Lebensqualität mittels des Short-Form-Health-Survey-12 (SF-12 Version 20) in einer deutschen Normstichprobe. *Zeitschrift fur Psychosomatische Medizin und Psychotherapie* **66**, 272–286 (2020).
52. Morfeld, M., Kirchberger, I. & Bullinger, M. *SF-36: Fragebogen zum Gesundheitszustand* 2nd edn. (Hogrefe, 2011).
53. Cotler, J., Holtzman, C., Dudun, C. & Jason, L. A. A brief questionnaire to assess post-exertional malaise. *Diagnostics* **8**(3), 66. https://doi.org/10.3390/diagnostics8030066 (2018).
54. Behrends, U. Screening auf post-exertionelle malaise (PEM). Fragebogen für Erwachsene (≥ 18 Jahre). Deutsche adaptierte Version des DSQ-Short-Form-PEM-Quesstionnaire-1. Technische Universität München (TUM) (2021).
55. Froehlich, L. et al. Medical care situation of people with myalgic encephalomyelitis/chronic fatigue syndrome in Germany. *Medicina* **57**(7), 646. https://doi.org/10.3390/medicina57070646 (2021).
56. Sykes, K. & Roberts, A. The Chester step test—A simple yet effective tool for the prediction of aerobic capacity. *Physiotherapy* **90**, 183–188 (2004).
57. Sevillano-Castaño, A. I. et al. Test-retest reliability and minimal detectable change in chester step test and 1-minute sit-to-stand test in long COVID patients. *Appl. Sci.* **13**, 8464 (2023).
58. Ghali, A. et al. The relevance of pacing strategies in managing symptoms of post-COVID-19 syndrome. *J. Trans. Med.* **21**, 375 (2023).
59. Parker, M. et al. Effect of using a structured pacing protocol on post-exertional symptom exacerbation and health status in a longitudinal cohort with the post-COVID-19 syndrome. *J. Med. Virol.* **95**, e28373 (2023).
60. Radbruch, L. et al. Validation of the German version of the brief fatigue inventory. *J. Pain Symptom Manag.* **25**, 449–458 (2003).
61. Robertson, R. J. et al. Validation of the adult OMNI scale of perceived exertion for cycle ergometer exercise. *Med. Sci. Sports Exerc.* **36**, 102–108 (2004).

62. Utter, A. C. et al. Validation of the Adult OMNI Scale of perceived exertion for walking/running exercise. *Med. Sci. Sports Exerc.* **36**, 1776–1780 (2004).
63. Jukic, I., Ramos, A. G., Helms, E. R., McGuigan, M. R. & Tufano, J. J. Acute Effects of cluster and rest redistribution set structures on mechanical, metabolic, and perceptual fatigue during and after resistance training: a systematic review and meta-analysis. *Sports Med.* **50**, 2209–2236 (2020).
64. Rappelt, L., Held, S., Leicht, M., Wicker, P. & Donath, L. Similar strength gains at lower perceived efforts via cluster set vs. traditional home-based online training: A 6 weeks randomized controlled trial. *Front. Sports Active Living* **4**, 968258 (2022).
65. Way, K. L. et al. cluster sets to prescribe interval resistance training: A potential method to optimise resistance training safety, feasibility and efficacy in cardiac patients. *Sports Med. Open* **9**, 86 (2023).
66. Lopes, T. R., Pereira, H. M. & Silva, B. M. Perceived exertion: Revisiting the history and updating the neurophysiology and the practical applications. *Int. J. Environ. Res. Public Health* **19**(21), 14439. https://doi.org/10.3390/ijerph192114439 (2022).
67. Shatz, I. Assumption-checking rather than (just) testing: The importance of visualization and effect size in statistical diagnostics. *Behav. Res. Methods* **56**, 826–845 (2024).
68. Gabrio, A., Plumpton, C., Banerjee, S. & Leurent, B. Linear mixed models to handle missing at random data in trial-based economic evaluations. *Health Econ.* **31**, 1276–1287 (2022).
69. Lüdecke, D., Ben-Shachar, M., Patil, I. & Makowski, D. Extracting, computing and exploring the parameters of statistical models using R. *JOSS* **5**, 2445 (2020).
70. Nordin, Å., Taft, C., Lundgren-Nilsson, Å. & Dencker, A. Minimal important differences for fatigue patient reported outcome measures-a systematic review. *BMC Med. Res. Methodol.* **16**, 62 (2016).
71. Singh, S. J. et al. Balancing the value and risk of exercise-based therapy post-COVID-19: a narrative review. *Eur. Respiratory Rev.* **32**(170), 230110. https://doi.org/10.1183/16000617.0110-2023 (2023).
72. Fietsam, A. C., Bryant, A. D. & Rudroff, T. Fatigue and perceived fatigability, not objective fatigability, are prevalent in people with post-COVID-19. *Exp. Brain Res.* **241**, 211–219 (2023).
73. Legler, F. et al. Long-term symptom severity and clinical biomarkers in post-COVID-19/chronic fatigue syndrome: Results from a prospective observational cohort. *EClinicalMedicine* **63**, 102146 (2023).
74. Hunter, S. K. Performance fatigability: Mechanisms and task specificity. *Cold Spring Harb. Perspect. Med.* **8**, a029728 (2018).
75. Kluger, B. M., Krupp, L. B. & Enoka, R. M. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology* **80**, 409–416 (2013).
76. Millet, G. Y. et al. Measuring objective fatigability and autonomic dysfunction in clinical populations: How and why?. *Front. Sports Active Living* https://doi.org/10.3389/fspor.2023.1140833 (2023).
77. Rudroff, T. The challenges of post-COVID-19 fatigue research. *Front. Psychol.* **14**, 1120928 (2023).
78. Tankisi, H., Versace, V., Kuppuswamy, A. & Cole, J. The role of clinical neurophysiology in the definition and assessment of fatigue and fatigability. *Clin. Neurophysiol. Pract.* **9**, 39–50 (2024).
79. Lemhöfer, C. et al. Quality of life and ability to work of patients with Post-COVID syndrome in relation to the number of existing symptoms and the duration since infection up to 12 months: A cross-sectional study. *Qual. Life Res. Int. J. Qual. Life Asp. Treat. Care Rehabilit.* **32**, 1991–2002 (2023).
80. Tarazona, V., Kirouchena, D., Clerc, P., Pinsard-Laventure, F. & Bourrion, B. Quality of life in COVID-19 outpatients: A long-term follow-up study. *J. Clin. Med.* **11**(21), 6478. https://doi.org/10.3390/jcm11216478 (2022).
81. Smith, P. et al. Post COVID-19 condition and health-related quality of life: a longitudinal cohort study in the Belgian adult population. *BMC Public Health* **23**, 1433 (2023).
82. Azzam, A. et al. The burden of persistent symptoms after COVID-19 (long COVID): A meta-analysis of controlled studies in children and adults. *Virol. J.* **21**, 16 (2024).
83. Yoon, J.-H. et al. The demographic features of fatigue in the general population worldwide: A systematic review and meta-analysis. *Front. Public Health* **11**, 1192121 (2023).
84. Pouliopoulou, D. V. et al. Rehabilitation interventions for physical capacity and quality of life in adults with post-COVID-19 condition: A systematic review and meta-analysis. *JAMA Netw. Open* **6**, e2333838 (2023).
85. Soares, M. N. et al. Skeletal muscle alterations in patients with acute Covid-19 and post-acute sequelae of Covid-19. *J. Cachexia Sarcopenia Muscle* **13**, 11–22 (2022).
86. Steiber, N. Strong or weak handgrip? Normative reference values for the German population across the life course stratified by sex, age, and body height. *PloS One* **11**, e0163917 (2016).
87. Vaishya, R., Misra, A., Vaish, A., Ursino, N. & D'Ambrosi, R. Hand grip strength as a proposed new vital sign of health: A narrative review of evidences. *J. Health Popul. Nutr.* **43**, 7 (2024).
88. Piotrowicz, K., Gąsowski, J., Michel, J.-P. & Veronese, N. Post-COVID-19 acute sarcopenia: Physiopathology and management. *Aging Clin. Exp. Res.* **33**, 2887–2898 (2021).
89. Silva, M. J. A. et al. Hyperinflammatory response in COVID-19: A systematic review. *Viruses* **15**(2), 553. https://doi.org/10.3390/v15020553 (2023).
90. Montes-Ibarra, M. et al. The impact of long COVID-19 on muscle health. *Clin. Geriatr. Med.* **38**, 545–557 (2022).
91. de Castro, G. S. et al. Post-COVID-19 condition: Systemic inflammation and low functional exercise capacity. *Front. Nutr.* **11**, 1295026 (2024).
92. Noonong, K. et al. Mitochondrial oxidative stress, mitochondrial ROS storms in long COVID pathogenesis. *Front. Immunol.* **14**, 1275001 (2023).
93. Guntur, V. P. et al. Signatures of mitochondrial dysfunction and impaired fatty acid metabolism in plasma of patients with post-acute sequelae of COVID-19 (PASC). *Metabolites* **12**(11), 1026. https://doi.org/10.3390/metabo12111026 (2022).
94. Martone, A. M. et al. Sarcopenia as potential biological substrate of long COVID-19 syndrome: Prevalence, clinical features, and risk factors. *J. Cachexia Sarcopenia Muscle* **13**, 1974–1982 (2022).
95. Hejbøl, E. K. et al. Myopathy as a cause of fatigue in long-term post-COVID-19 symptoms: Evidence of skeletal muscle histopathology. *Eur. J. Neurol.* **29**, 2832–2841 (2022).
96. Appelman, B. et al. Muscle abnormalities worsen after post-exertional malaise in long COVID. *Nat. Commun.* **15**, 17 (2024).
97. Colosio, M. et al. Structural and functional impairments of skeletal muscle in patients with postacute sequelae of SARS-CoV-2 infection. *J. Appl. Physiol. (Bethesda, Md.: 1985)* **135**, 902–917 (2023).
98. Agergaard, J. et al. Myopathy as a cause of Long COVID fatigue: Evidence from quantitative and single fiber EMG and muscle histopathology. *Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol.* **148**, 65–75 (2023).
99. San-Millán, I. The key role of mitochondrial function in health and disease. *Antioxidants* **12**(4), 782. https://doi.org/10.3390/antiox12040782 (2023).
100. Burini, R. C., Anderson, E., Durstine, J. L. & Carson, J. A. Inflammation, physical activity, and chronic disease: An evolutionary perspective. *Sports Med. Health Sci.* **2**, 1–6 (2020).
101. Gleeson, M. et al. The anti-inflammatory effects of exercise: Mechanisms and implications for the prevention and treatment of disease. *Nat. Rev. Immunol.* **11**, 607–615 (2011).
102. Gao, J., Pan, X., Li, G., Chatterjee, E. & Xiao, J. Physical exercise protects against endothelial dysfunction in cardiovascular and metabolic diseases. *J. Cardiovasc. Transl. Res.* **15**, 604–620 (2022).
103. Luo, B. et al. The anti-inflammatory effects of exercise on autoimmune diseases: A 20-year systematic review. *J. Sport Health Sci.* **13**, 353–367 (2024).

104. Vøllestad, N. K. & Mengshoel, A. M. Post-exertional malaise in daily life and experimental exercise models in patients with myalgic encephalomyelitis/chronic fatigue syndrome. *Front. Physiol.* **14**, 1257557 (2023).
105. Tryfonos, A. et al. Functional limitations and exercise intolerance in patients with post-COVID condition: a randomized crossover clinical trial. *JAMA Netw. Open* **7**, e244386 (2024).
106. White, P. D. et al. Anomalies in the review process and interpretation of the evidence in the NICE guideline for chronic fatigue syndrome and myalgic encephalomyelitis. *J. Neurol. Neurosurg. Psychiatry* **94**, 1056–1063 (2023).
107. White, P. D., Sharpe, M. & Chalder, T. Evidence-based care for people with chronic fatigue syndrome and myalgic encephalomyelitis. *J. General Intern. Med.* **37**, 3195 (2022).
108. Ladlow, P., Bennett, A. N. & O'Sullivan, O. Exercise therapy for post-COVID-19 condition-does no harm. *JAMA Netw. Open* **7**, e246959 (2024).
109. Stussman, B. et al. Characterization of post-exertional malaise in patients with myalgic encephalomyelitis/chronic fatigue syndrome. *Front. Neurol.* **11**, 1025 (2020).
110. Weigel, B., Eaton-Fitch, N., Thapaliya, K. & Marshall-Gradisnik, S. Illness presentation and quality of life in myalgic encephalomyelitis/chronic fatigue syndrome and post COVID-19 condition: a pilot Australian cross-sectional study. *Qual. Life Res. Int. J. Qual. Life Aspects Treat. Care Rehabil.* https://doi.org/10.1007/s11136-024-03710-3 (2024).
111. DSSV Arbeitgeberverband Deutscher Fitness- und Gesundheits-Anlagen. Eckdaten der Deutschen Fitnesswirtschaft (2024).

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A.B.: Writing—original draft, Data curation, Formal analysis, Methodology, Investigation, Project administration; J.B.: Writing—original draft, Data curation, Formal analysis, Methodology, Investigation, Project administration; M.S.: Software, Data curation, Formal analysis, Writing—review and editing; A.M.: Conceptualization, Writing—review and editing, Methodology; M.W.: Conceptualization, Writing—review and editing; J.R.: Conceptualization, Supervision, Writing—review and editing; J.J.: Supervision, Writing—review and editing.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval and consent to participate
The study was approved by the ethics committee of the Medical Association responsible (identification number 07/23) and was conducted in accordance with the Declaration of Helsinki[46]. It was registered in the German Clinical Trials Register (ID: DRKS00031634) a priori. All participants gave written informed consent before participating in the study.

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