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Review Article

Using Exercise Therapy for Long COVID Without Screening for Post-Exertional Symptom Exacerbation Potentially Increases the Risks for Patients Who Suffer from it: A Reanalysis of Three Systematic Reviews

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Abstract

Background: Three systematic reviews all concluded that exercise is an effective treatment for long COVID.

Objective: To determine if exercise therapy is also an effective treatment for long COVID patients who suffer from Post-Exertional Malaise (PEM) or Post-Exertional Symptom Exacerbation (PESE).

Method: The authors analyzed the evidence from three systematic reviews, and the trials in it, that all concluded that exercise is an effective treatment for long COVID.

Results and Discussion: Our reanalysis shows that there were a number of important issues with these reviews. The first systematic review reviewed the literature and investigated the benefits of exercise in healthy people. These were then extrapolated to long COVID even though one can only say something about the efficacy of a treatment for a particular condition if that treatment is actually investigated for that particular condition. The second systematic review included 32 exercise studies, yet 22 of those did not have a control group and only three of the remaining ten investigated exercise therapy for long COVID. The third systematic review included seven exercise studies for long COVID, yet five of them did not have a control group. Any causal inference about the efficacy of a treatment is impossible because of that.

The treatment groups in the remaining five studies from both systematic reviews were all small to very small. Additionally, all five studies used a badly designed control group. The proportion of PEM/PESE was not described by the studies or the systematic reviews, and none of the trials described the severity of it. It is unclear why they didn't do that because the potentially harmful effects of exercise therapy for patients who suffer from PEM/PESE have been documented by many studies including the Living Guidance for Clinical Management of COVID-19 by the World Health Organization. Many health professionals think that post-exertional fatigue, i.e. tiredness after exercise, is PEM/PESE even though tiredness after exercise is simply a normal physiological response to exercise. The following four elements are essential for a diagnosis of PEM/PESE:

A. a disproportional worsening of symptoms,

B. following trivial physical or mental exertion,

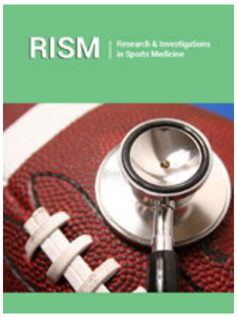
C. with loss of strength and/or loss of function,

D. and an abnormally delayed recovery.

Conclusion: The three systematic reviews do not provide any evidence that exercise therapy is a safe and effective treatment for long COVID patients who suffer from PEM/PESE. Gradually increasing exercise is not an effective treatment for PESE/PEM, instead it is a diagnostic test, albeit a very harmful one which in the absence of effective pharmacological treatments, can render people bedridden for life. Consequently, patients who do suffer from PEM/PESE cannot do it, and patients who can do it, have been wrongly diagnosed with PEM/PESE. Additionally, the medical profession potentially increases the risks for the health of long COVID patients who suffer from PEM/PESE, by not excluding those patients from exercise trials.

Keywords: COVID-19; Exercise intolerance; Long COVID; Post-COVID-19 condition; PEM; PESE; Post-exertional malaise; Post-exertional symptom exacerbation

ISSN: 2577-1914



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Submission: October 01, 2024

Published: October 23, 2024

Volume 10 - Issue 5

How to cite this article: Mark Vink* and Friso Vink-Niese. Using Exercise Therapy for Long COVID Without Screening for Post-Exertional Symptom Exacerbation Potentially Increases the Risks for Patients Who Suffer from it: A Reanalysis of Three Systematic Reviews. Res Inves Sports Med. 10(5), RISM.000748. 2024.
DOI: 10.31031/RISM.2024.10.000748

Introduction

The World Health Organization (WHO) published its clinical case definition of post-COVID-19 condition (commonly known as long COVID) by a Delphi consensus in April 2022 because "the absence of a globally standardized and agreed-upon definition hampers progress in characterization of its epidemiology and the development of candidate treatments" (p. e102 [1]). The WHO defined Post COVID-19 Condition as the continuation or development of new symptoms, 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation. It can affect anyone exposed to SARS-CoV-2, regardless of age or severity of original symptoms. Persistent (chronic) fatigue is consistently reported to be the most prevalent symptom of long COVID [2]. Common other symptoms which may fluctuate or relapse over time, are cognitive dysfunction, dyspnoea, exercise intolerance and Post-Exertional Symptom Exacerbation (PESE) which is often referred to as Post-Exertional Malaise (PEM), sleep disorders, and myalgia [3-5]. Reports of symptoms that worsen in response to exertion have led to comparisons between long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), another post-infectious disease. ME/CFS is characterized by PEM or PESE, a worsening of symptoms, and reduction in function after physical, cognitive, or emotional activity that would not have caused a problem before illness. An observational study by Twomey et al. [3] (n=213) found that 58.7% of the long COVID patients in their study suffered from PEM [3]. A study into the prevalence of ME/CFS in long COVID patients (n=465) found that 58% met a ME/CFS case definition [6]. A recent article about the clinical characteristics of Long COVID patients presenting to a dedicated academic post-COVID-19 clinic in Texas (n=252), noted the following: "Although we did not directly screen for ME/CFS, based on survey responses, we estimate that at least 60% of our cohort would meet the [ME/CFS] diagnostic criteria" (p. 5 [7]). Choutka et al. [8] which included immunologist Iwasaki, noted the following: the "similar symptom profiles of individual PAISs [post-acute-infection syndromes], irrespective of the infectious agent, as well as the overlap of clinical features with…ME/CFS, suggest…a common etiopathogenesis" (p. 911 [8]).

In March 2023, Davis et al. [5] concluded in their review of the current evidence about long COVID that "there are currently no validated effective treatments" (p. 134 [5]). Thereby confirming the conclusion from the WHO from a year before [9]. However, a review by Sick & König [10] concluded in August 2023 that "exercise enhanced aerobic fitness and physical function and relieved symptoms of dyspnea, fatigue and depression" in long COVID and that "the exercise programs were well tolerated with no adverse events" (p. 1 [10]). At the same time a review by Torres et al. [11] concluded that "this review describes the evidence of how exercises can mitigate the effects of COVID-19 in each organ system that the virus affects" (p. 284 [11]). But also, that "evidence presented in the review suggests that "exercise should be considered a first-line strategy in the prevention and treatment of COVID-19 infection and long COVID disease" (p. 284 [11]). Torres & Gradidge [12] concluded in September 2023 in their systematic review and meta-analysis of thirty-two exercise studies, that "rehabilitation interventions significantly improve cardiorespiratory fitness and pulmonary function in post-COVID-19 infection patients" (p. 1 [12]). Long COVID Scientific Consultant Carroll, together with Harvey, responded to the article by Torres et al. [11] entitled "Exercise Is the Most Important Medicine for COVID-19" and raised a number of issues with that including the following. "Whilst estimates vary, approximately 50% of long-COVID patients suffer with Myalgic Encephalomyelitis (ME). Exercise is contraindicated in clinical guidelines for ME due to risk of Post Exertional Neuroimmune Exhaustion (PENE) which can in some cases lead to permanent worsening" (p. 423 [13]). Torres et al. [14] dismissed this argument stating that "the Centers for Disease Control and Prevention have stated the following: While vigorous aerobic exercise can be beneficial for many chronic illnesses, patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) do not tolerate such exercise routines. However, it is important that patients with ME/CFS maintain activities that they can tolerate since deconditioning is harmful to patients. Patients who are tolerating their current level of activity and have learned to listen to their bodies might benefit from carefully increasing exercise to improve their physical fitness and avoid deconditioning. Some health care providers with expertise in ME/CFS refer their patients to an exercise physiologist who understands ME/CFS and uses an individualized and flexible approach to advancing activity levels. Thus, as authors we do not agree that exercise is totally contraindicated for ME" (p. 424 [14]). However, increasing exercise to improve physical fitness doesn't work for patients with ME/CFS because their limits are fixed and if they go over their limits that triggers PENE/PESE which leads to symptom exacerbations and relapses. The conclusion by the three aforementioned systematic reviews, however, is diametrically opposed to the conclusion by the WHO but also to the lived experience of patients. In this article, we will review the three aforementioned systematic reviews and analyze the trials in it, which they used as evidence regarding the safety and efficacy of exercise therapy, to see if there is any merit in it or if the systematic reviews should have come to a different conclusion. This is especially important, because, the WHO's Clinical management of COVID-19: living guideline, Version 7, currently recommends that healthcare professionals should be "excluding PESE before commencing exercise therapy, and [they should be] careful monitoring for PESE both during and after exercise" (p. 116 [15]). Or to put it differently, the WHO recommends that healthcare professionals should not use exercise therapy for long COVID patients who suffer from PESE.

Analysis of the Three Systematic Reviews

Torres et al. [11] (Review entitled: "Exercise is the most important medicine for COVID-19")

Torres et al. [11] concluded that "exercises can mitigate the effects of COVID-19 in each organ system that the virus affects. The evidence presented in the review suggests that exercise should be considered a first-line strategy in the prevention and treatment of COVID-19 infection and long COVID disease" (p. 284 [11]). Torres et al. [11] conducted a review of the literature, which was in large part, a review of the literature on the benefits of exercise in healthy people which was then extrapolated to long COVID patients. This was acknowledged by the authors in the article when they stated that “it should be noted that the evidence exists for nonCOVID-19 patients and needs to be verified in COVID-19 and long COVID patients” (p. 287 [11]). Moreover, nowhere in the systematic review is the presence of PESE taken into account. Consequently, no evidence is presented that exercise is a safe and effective treatment for individuals who have long COVID and are suffering from PESE.

Sick & König [10] (Review entitled: “Exercise training in non-hospitalized patients with post-COVID-19 syndrome-a narrative review”)

Sick & König [10] reviewed 7 studies and concluded in August 2023 that “exercise enhanced aerobic fitness and physical function and relieved symptoms of dyspnea, fatigue and depression” in long COVID and that “the exercise programs were well tolerated with no adverse events” (p. 1 [10]). They also concluded that “caution is advised when working with patients suffering from post-exertional malaise or diagnosed with myalgic encephalomyelitis/chronic fatigue syndrome” (p. 1 [10]).

Lack of a control group/badly designed control group: Five of the seven studies in the review did not have a control group. Why this was not flagged up by the systematic review as a problem is unclear because four of the studies themselves did. The one notable exception being the “prospective, observational, single-center study” by Ostrowska et al. (p. 2 [16]). Estebanez-Pérez et al. [17] noted the following about this. “The greatest disadvantage of quasi-experimental studies is that randomization is not used, limiting the study’s ability to conclude a causal association between an intervention and an outcome” (p. 11 [17]). Nopp et al. [18] noted that a major limitation of their study was the fact that “no causal role of rehabilitation can be assumed with certainty due to our observational study design”. They continued by saying that “therefore, the observed improvement in the primary and secondary endpoints might also be due to the normal recovery process or regression to the mean” (p. 599 [18]). Finally, Smith et al. [19] stated that “some limitations must be acknowledged. First, a control group was not included. Therefore, we cannot directly attribute all of the observed benefits to the LC rehabilitation program or understand the influence of factors such as support from Rehabilitation Specialists or social interaction with other participants” (p. 08 [19]). However, they then try to downplay what they have just stated themselves with the following: “nonetheless, the observed benefits exceed any improvements reported without intervention in the literature” (p. 08 [19]).

Something similar was concluded by Hasenoehrl et al. [20] who first note that “a study limitation is the lack of an inactive control group” but then play that down in a similar manner to Smith et al. [19] by stating the following. “When considering the extent of the improvements both of physical performance as well as the post COVID functional status within all individuals, it is safe to assume that the measured improvements directly result from the exercise intervention” (p. 6 [20]). Yet, because these studies did not have a control group, none of the observed benefits can be attributed to the treatment, irrespective of “the extent of the improvements”. Because as earlier noted by Estebanez-Pérez et al. [21] without a control group, one cannot come to any conclusion about a causal association between an intervention and an outcome. The other two studies used a no treatment control group. A key principle of a Randomized Controlled Trial (RCT) to ensure a fair comparison is that groups should be similar with respect to all factors that might affect the outcome, besides the intervention, including the number of treatment sessions, to ensure a fair comparison but, also, to make sure that an RCT is ‘internally valid’, which refers to the extent that the outcome for a trial can be attributed to the experimental treatment and not to any alternative explanation, such as the natural course of the target problem [22]. Yet, in a no treatment control group, patients do not get any treatment from (a doctor from) that study which renders a fair comparison impossible.

Also, in a no treatment, SMC or Waiting List Control Group (WLC), participants must attend several assessments without any direct benefit for themselves. These patients will be disappointed that they have been denied treatment benefits they anticipated from participation in a study. Assignment to those sort of control groups may strengthen participants’ beliefs that they will not improve, thereby reducing the chance of spontaneous improvement [22]. Researchers often assume that with waiting list control groups and other no-treatment control designs, the absence of treatment equates with the absence of an effect. Yet participants randomized to these designs may improve less than would be expected compared to participants not enrolled in a trial which may threaten the internal validity of a trial. Consequently, subjective baseline-follow-up differences cannot be assumed to be the natural history of what would have occurred in the absence of patients enrolling in the study [22]. Also, using waitlist, usual care or no-treatment control conditions does not adequately correct for the placebo effect, regression to the mean and other forms of biases and confounding factors [22-24]. Moreover, as concluded by Boot et al. [25] “measuring the effectiveness of…[a]…therapy by comparing it with a no-treatment control condition would be inadequate because the two groups would have different expectations for improvement” (p. 445 [25]). “Active control groups are superior to “no-contact” controls, only when the active control group has the same expectation of improvement as the experimental group can we attribute differential improvements to the potency of the treatment” (p. 445 [25]). Yet researchers “persist in drawing inappropriate inferences from designs that lack adequate controls. Without measuring and controlling for placebo effects, such studies provide little more than speculation about the causes of improvements” (p. 452 [25]).

Additionally, Lane et al. [26] from the Research Centre for Sport, Physical Activity (SPARC) from the University of Wolverhampton, published a study in the journal Sports. In it they examined the effects of using an active-control group, “in which basic instructions are repeated and so attempts to control for belief effects” (p. 6 [26]) in comparison to a no-treatment group. “Results demonstrated that the no-treatment group performed significantly worse, made less progress…than the active-control and active-treatment groups" (p. 5 [26]). Therefore, using waitlist, usual care or no-treatment control conditions can lead to the overestimation of the effectiveness of a treatment [22]. This highlights the importance of having studies with well-designed control groups. In a study with a well-designed control group, the only difference between the control and treatment group, is the treatment under investigation. Everything else, including the expectation raised about the efficacy of the control treatment, should be the same as in the treatment group. That way, there are no other factors influencing the results and consequently any effect can only be down to the treatment under investigation.

Sample size: A review of homeopathy studies by the Australian National Health and Medical Research Council (NHMRC), used a minimum number of 150 participants in randomized controlled trials (evenly distributed across the therapy and control group) because, according to the NHMRC, the results may be distorted in studies with a smaller number of participants [27]. Consequently, 'trials with limited sample sizes are more likely to report larger beneficial effects than large trials" (p. 1 [28]). This is also known as the small study effect. We not only mention this review by the NHMRC because of the distortion of results if the number of participants in a study is small (less than 75 in the treatment group), but also because it was an integral part of the recent advice of the EASAC Homeopathy Working Group-The European Academies Science Advisory Council-to the EU on homeopathy [29]. In the two studies that did have a control group, the number of participants in the treatment groups was small (19 and 20, respectively) as can be seen in Table 1. Consequently, one should be careful with interpreting therapeutic responses in those RCTs because any improvement might simply be down to the small study size and not to the treatment under investigation. Also, these two studies would have been excluded from the recent advice of the EASAC Homeopathy Working Group for having less than the minimum number of participants in the treatment group. Moreover, both these two studies used a no treatment control group which might have artificially inflated the treatment effect because it's known that comparing a treatment to passive controls produces bigger relative effect sizes, than when it's compared to an active control condition [30-32].

Table 1: Study characteristics and percentages with PEM in Sick & König [10].

Study	Study Type	Diagnosis	N	Intervention	Control Group	% with PEM Assessed	Separate Reporting of Results for those with and without PEM
Estebanez-Pérez et al. [17]	Non-randomised study	Long COVID	32	A 4-week digital physiotherapy practice intervention with an individualised and customise exercise programme	No control group	No	No
Hasenoehrl et al. [20]	Non-randomised study	Post COVID fatigue in healthcare workers	32 (severe SSG, n=11; mild MSG, n=21)	Physical exercise (advised to perform as much aerobic exercise as feasible)	No control group	No	No
Jimeno-Almazán et al. (Rehabilitation study) [34]	RCT	Post-COVID condition after mild COVID-19 in non- hospitalized patients	39	Supervised exercise (n=19)	No treatment (n=20)	No	No
Jimeno-Almazán et al. (RECOVE trial) [33]	Randomized clinical trial	Post-COVID-19 conditions after mild COVID-19	80	1) multicomponent exercise program (n=20); 2) inspiratory muscle training (n=17); 3) a combination of both of the above (CTRM, n=23)	No treatment (n=20)	No	No
Nopp et al. [18]	Non-randomised study	Long COVID	64	a 6-week interdisciplinary individualized pulmonary rehabilitation program	No control group	No	No
Ostrowska et al. [16]	Non-randomised study	Long COVID	97	a six week multidisciplinary rehabilitation program	No control group	73% reported exercise intolerance	No
Smith et al. [19]	Non-randomised community rehabilitation program	Long COVID	601	12 week rehabilitation program including three exercise sessions, consisting of aerobic and strength base exercises	No control group	No	No

Post Exertional Malaise (PEM or PESE): Jimeno-Almazán et al. [33] noticed in their RECOVE study that "long COVID or post-COVID-19 syndrome…[is]…characterized by a varied set of symptoms such as fatigue, post exertional malaise, shortness of breath (dyspnea), cognitive impairment, headache and musculoskeletal pain, among others" (p. 95 [33]). Estebanez-Pérez et al. [17] state that "in 2020, the WHO published guidelines for those patients who continue to suffer from the long-term consequences of COVID-19 and provides guidance on rehabilitation" and that "the exercise intensity should not be pushed because of the risk of post-exercise fatigue. A gradual increase in exercise should be based on symptoms" (p. 2 [17]). Yet, despite stating that, both studies did not investigate how many patients in their study suffered from PESE or PEM. Nor did they exclude those patients or report results separately for those with and those without PESE or PEM. The other five studies in the systematic review didn't do that either. Why they didn't do that is unclear. This is particularly worrisome as the large non-controlled study by Smith et al. [19] (n=601) used a "12-week program included three exercise sessions per week consisting of aerobic and strength-based exercises" (p. 01 [19]) and in Hasenoehrl et al. [20] participants "were advised to perform as much aerobic exercise as feasible, but at least complete three times 20min of moderate aerobic exercise per week" (p. 3 [20]).

In Ostrowska et al. [16] "the majority of patients reported exercise intolerance (73.2%), followed by sleep disturbances (46.9%) and fatigue (39.2%)" (p. 4 [16]). The researchers do not elaborate on what exercise intolerance entails. Did patients have reduced fitness because of having been ill with COVID-19, or did they suffer from Post Exertional Symptom Exacerbation (PESE) or a combination of the two? It is unclear why the studies, especially those who were using aerobic exercise as part of their intervention, didn't investigate how many patients in their study suffered from PESE/PEM before starting treatment. As it is known from ME/CFS, which is characterized by PESE/PEM, that aerobic exercises lead to symptom exacerbations and relapses, and are therefore contraindicated.

Six-minute walk test (6MWT)/fitness: In Hasenoehrl et al. [20], the average age in the mild symptom group (MSG) was 42.9 compared to 47.4 in the severe symptom group (SSG), 60% (MSG) and 89% (SSG) were female, the VO2max (ml/kg/min) at baseline was 33.8 (MSG) and 30.4 (SSG) and patients walked 656.3m (MSG) and 632.0m (SSG) on the 6MWT. Consequently, before starting treatment, the 6MWT scores were in the normal range and the VO2 max scores were in the lower part of the normal range. This suggests that the participants were only very mildly affected by long COVID.

In Jimeno-Almazán et al.'s [34] rehabilitation study the mean age was 44.6 (rehabilitation) and 46.0 (control), 68% (rehabilitation) and 80% (control) were female and the VO2 max scores were 36.8 (rehabilitation) and 36.4 (control). This study did not use the six-minute walk test, but its baseline VO2max scores suggest that the fitness of patients was already in the normal range before starting treatment. Moreover, as noted by the researchers themselves, "A relevant number of participants were receiving treatment for mood disorders and significant reductions in physical activity have been found in the population before limiting the effectiveness of the results in exercise projects" (p. 9 [34]). An umbrella review by Singh et al. [35] concluded that "physical activity is highly beneficial for improving symptoms of depression, anxiety and distress across a wide range of adult populations, including the general population, people with diagnosed mental health disorders and people with chronic disease. Physical activity should be a mainstay approach in the management of depression, anxiety and psychological distress" (p. 1 [35]). Consequently, any improvement in the treatment group could merely reflect an improvement in the symptoms of depression, anxiety and/or psychological distress. Additionally, "both exercise and control groups experienced a similar reduction in the total number of symptoms after the 8-week period" (p. 5 [34]). This raises further doubt about the efficacy of the treatment.

In Ostrowska et al. [16] the authors concluded that the rate of improvement on the six-minute walk test, was more than 90% even though an improvement from "320m before starting the physical training program to 382.5m" (p. 6 [16]) equates to an improvement of 19.5% (62.5/320) and not more than 90%. Moreover, the study did not have a control group and "cardiopulmonary exercise test did not show any change" (p. 1 [16]). The learning effect in the 6MWT-better performing on the second test because of familiarity with the test-in 761 patients with severe emphysema (mean age of 67, 10% requiring oxygen at rest and 77% during the test) was 7 per cent and in patients with hypoxemia from COPD and restrictive lung diseases, it was 14.9 per cent [36]. Stevens et al. [37] performed three 6MWTs in COPD patients to see how much patients would improve by simply repeating the test on consecutive days. They found a learning effect (a mean increase) of 10 per cent on the second test and an additional 3 per cent on the third test. The improvement in Ostrowska et al. [38] is in stark contrast with patients with stable chronic heart failure, who improved their 6MWT results by 65 per cent after only 3 weeks of exercising. This suggests that the improvement on the six-minute walk test did not reflect a real improvement, but merely a change in scores because of the learning effect in the 6MWT and/or learning to optimize how far they could work in the rehabilitation program which "was composed of physical training (aerobic, resistance, and breathing exercises), education, and group psychotherapy" (p. 1 [16]).

Torres & Gradidge [12] (Review entitled: "The quality and pattern of rehabilitation interventions prescribed for post-COVID-19 infection patients: A systematic review and meta-analysis")

Problems with the control group: Torres & Gradidge [12] concluded that "rehabilitation interventions significantly improve cardiorespiratory fitness and pulmonary function in post-COVID-19 infection patients; however, there is a need for conceptualizing high-quality and long-term rehabilitation interventions, especially exercise interventions" (p. 1 [12]). Table 2 highlights the characteristics of the studies in the systematic review. Almost all the studies used a no treatment control group which, as discussed earlier, can artificially inflate the efficacy of a treatment. In three of the ten studies, patients had been ill for three months or more and thereby would be classed as long COVID patients. In one study, it is unclear how long patients have been ill, and in the other six, formerly hospitalized patients were treated after discharge from hospital. The three studies in this systematic review that tested the efficacy of exercise therapy for long COVID were the studies by Jimeno-Almazán et al. [34], Li et al. [39] & McNarry et al. [40]. The rehabilitation study by Jimeno-Almazán et al. [34] was also included in the systematic review by Sick & König [10] and was discussed there. The primary outcome of Li et al. [39] was the six minute walk test. Therefore, this study will be discussed under the six-minute walk test heading.

Table 2: Study characteristics and percentages with PEM in Torres & Gradidge [12].

Study	Study Type	Diagnosis	Ill less than Three Months	N	Intervention	Control Group	% with PEM Assessed	Separate Reporting of Results for those with and without PEM
Abodonya et al. [41]	Prospective pilot clinical study	Recovered ICU COVID-19 patients after weaning from mechanical ventilation	Yes	42	Inspiratory muscle training (n=21)	No treatment (n=21)	No	No
Hameed et al. [42]	Non-randomized outpatient virtually delivered pulmonary rehabilitation program	Persistent COVID-19 symptoms in formerly hospitalised patients	Yes	106	Virtual physical therapy (n=44); home physical therapy (n=25); independent exercise program (n=17);	No treatment (n=20)	No	No
Jimeno-Almazán et al. (rehabilitation study) [34]	RCT	Post-COVID condition after mild COVID-19 in non- hospitalized patients	No, ill for 29 weeks	39	Supervised exercise (n=19)	No treatment (n=20)	No	No
Li et al. [39]	RCT	Formerly hospitalised patients with remaining moderate dyspnoea	No, ill for 103 days	120	Telerehabilitation programme (n=59)	No treatment (n=61)	No	No
Liu et al. [43]	RCT	Formally hospitalised elderly patients (mean age 69)	Yes	76	Respiratory rehabilitation, (n=38)	No treatment (n=38)	No	No
McNarry et al. [40]	RCT	Long COVID.	No, 9 months post acute Covid	224	Inspiratory Muscle Training (n=176)	Waitlist (n=48)	No	No
Okan et al. [44]	RCT	Post-COVID-19 dyspnea	Unclear	52	Breathing exercises given by telemedicine (n=26)	Brochure explaining the exercises (n=26)	No	No
Ozlü et al. [45]	RCT	Inpatients from a normal ward (no one spend time on an intensive care ward) with moderate and severe COVID-19 pneumonia who were ready to be discharged	Yes, ill for 14 to 21 days	86 but study only reported the 82 who completed follow up	Home exercise program (n=42)	No treatment (n=40)	No	No
Pehlivan et al. [46]	RCT	Formally hospitalised patients who had been discharged less than four weeks ago	Yes	40	Telerehabilitation consisting of breathing and range of motion exercises, and aerobic training (n=20)	Patients received an exercise brochure (n=20)	No	No

Srinivasan et al. [47]	RCT	Formerly hospitalised patients with remaining dyspnoea	Yes	48	Pursed lip breathing exercise with bhastrika pranayama (n=24)	Breathing exercise with incentive spirometry (n=24)	No	No

McNarry et al. [40] concluded that Inspiratory Muscle Training (IMT) enhances recovery post COVID-19. Yet the estimated VO2max scores at baseline were 37.9 in the control group and 37.5 in the IMT treatment group. This indicates that the participants had normal fitness at baseline. Moreover, 37% of patients from the treatment group (65/176) were lost to follow-up which suggests that the treatment was not effective or very well tolerated by them. In reality, this might have been a lot higher because of the large number of participants (48) who were randomized and allocated to treatment, yet did not start the treatment. If those participants would be included, then, 50.4% (113/224) of participants allocated to the intervention, didn't find the intervention helpful and/or acceptable. Moreover, the study used a no treatment control group which is known to artificially inflate a treatment effect raising more doubts about the efficacy of the treatment.

Sample size: Most studies had a fairly small number of participants in the treatment group, ranging from 20 to 45 with the noticeable exception of McNarry et al. [40], which treated 176 patients with long COVID with Inspiratory Muscle Training yet used a waitlist control group as can be seen in Table 2. Jimeno-Almazán et al. [34] noted that one of the limitations of their study was "the sample size" (p. 102 [34]) with only 19 participants in the exercise treatment group. Consequently, one cannot conclude anything about the efficacy of their treatment.

Post Exertional Malaise (PEM or PESE): The aforementioned study by Twomey et al. [3], which found that 58.7% of people with long COVID suffer from PEM, concluded in January 2022 that "PEM is a significant challenge for this patient group. Because of the potential for setbacks and deteriorated function following overexertion, fatigue and post exertional symptom exacerbation must be monitored and reported in clinical practice and in studies involving interventions for people with long COVID" (p. 1 [3]). Yet none of the studies investigated/assessed how many participants were suffering from PEM / PESE as can be seen in Table 2. As a consequence, none of these studies reported results separately for those with and for those without PEM/PESE. Why the studies, especially those which were using aerobic exercise as part of their intervention, did not do so, is unclear.

Six Minute Walk Test (6MWT)/fitness: Torres & Gradidge [12] partly based the efficacy of exercise on their conclusion, that "there was a significant difference in the 6-minute walk test… (51.69m)" (p. 1 [12]). Two of the three long COVID studies in this systematic review, Jimeno-Almazán et al. & McNarry et al. [34,40], did not use the six-minute walk test as an outcome, as can be seen in Table 3. The only other long COVID study in this systematic review, the study by Li et al. [39] did and they noted that, "limitations of this research [their study] include participant characteristics: only COVID- 19 survivors with moderate dyspnoea symptoms who had previously been hospitalized for treatment were included. The results are thus not generalizable to persons with mild or severe dyspnoea, nor to people who contracted SARS CoV- 2 but were not hospitalized" (p. 703 [39]). Furthermore, with a few exceptions, this trial was executed according to the original protocol (p. 702, 703 [39]). Yet they do not state what those changes to the protocol are and how they might have affected the outcome. Li et al. [39] also noted that the "length of inpatient stay was longer and the proportion of patients with severe COVID- 19 was somewhat greater in the intervention group which may have enabled a larger effect size" (p. 703 [39]).

The primary outcome of the study "was functional exercise capacity at post-treatment measured with the 6min walking test (6MWT)" (p. 698 [39]) and even though patients with a mean age of 49 (treatment group) were suffering from moderate shortness of breath, the mean distance walked in the 6MWT in meters was 515m (treatment group); 46% of participants were male and 54% female. A study by Cazzoletti et al. [48] was set up "to determine the reference equations to predict the 6MWD [6-minute walk distance, i.e. the distance walked in six minutes] in a large Italian population sample of healthy adults" (p. 1 [48]). They noted that "the 6-min walk distance test is a quick, easy and inexpensive tool for measuring functional exercise capacity" and "quality of life" (p. 1 [48]). The study included 287 healthy females and 243 healthy males with a mean age of 46 and 47, respectively, which is very similar to the mean age of 49.17 in Li et al. [39]. Healthy females walked 581m and healthy males 609m. Consequently, the patients in Li et al. [39] were already fairly high functioning before starting treatment. Moreover, the study itself concluded that after treatment, "no group differences were found for lung function" (p. 697 [39]). Additionally, 39% of participants from the treatment group were lost to follow up. People who drop out are usually the ones who do not benefit from a treatment and/or are negatively affected by it. An improvement of 65.45m on the six-minute walk test when patients in the treatment group already walked 515m at baseline equates to 12.7%. Consequently, this improvement could simply be a reflection of the learning effect as discussed earlier and/or a reflection of the fact that there were less than 75 participants in the treatment group in this study in combination with the very high dropout rate.

Table 3: Effect on six-minute walk test and work status in Torres & Gradidge [12].

Study	Diagnosis	Intervention	6-MWT Improvement over the Control Group	Work Status before and after Treatment	Loss to Follow up
Abodonya et al. [41]	Recovered ICU COVID-19 patients after consecutive weaning from mechanical ventilation	Inspiratory muscle training	39m	Not reported	0% in both groups
Hameed et al. [42]	Persistent COVID-19 symptoms after hospitalisation	Virtual physical therapy, home physical therapy and an independent exercise program	Not used	No differences across groups (differences in return to work were "not statistically significant" p.615)	50% in all 4 groups
Jimeno-Almazán et al. (Rehabilitation study) [34]	Post-COVID condition after mild COVID-19 in non- hospitalized patients	Supervised exercise	Not used	Not reported	Not reported
Li et al. [39]	Remaining moderate dyspnoea complaints after hospitalisation	Telerehabilitation	65m	Not reported	Telerehabilitation 39% (23/59); control group, 8% (5/61)
Liu et al. [43]	Formerly hospitalised elderly patients	Respiratory rehabilitation	48m	Retired people	Respiratory rehabilitation, 5% (2/38); control group 5% (2/38)
McNarry et al. [40]	Long COVID	Inspiratory Muscle Training (IMT)	Not used	Not reported	IMT 37% (65/176); control group 23% (11/48)
Okan et al. [44]	Post-COVID-19 dyspnea	Breathing exercises given by telemedicine	49m	Not reported	Unclear
Ozlü et al. [45]	Inpatients who were ready to be discharged	Home exercise program	Not used	Not reported	5% (4/86) but not reported from which groups
Pehlivan et al. [46]	Formerly hospitalised patients	Telerehabilitation	Not used	Not reported	15% in both groups (3/20)
Srinivasan et al. [47]	Formerly hospitalised patients with remaining dyspnoea	Pursed lip breathing exercise with bhastrika pranayama	Not used	Not reported	Not reported

Discussion

Effective treatments or no effective treatments for long COVID?

In March 2023, Davis et al. [5] concluded in their long COVID review that "there are currently no validated effective treatments" (p. 134 [5]). Thereby confirming the conclusion from the WHO from a year before [9]. A population based longitudinal cohort study by Ballouz et al. [49] (1106 adults with a confirmed SARS-CoV-2 infection who were not vaccinated before infection compared to 628 healthy controls) found that "fatigue, post-exertional malaise, altered taste or smell, dyspnoea, and reduced concentration or memory were the most prevalent symptoms at all time points" (p. 9 [49]). Also, that 22.9% of individuals infected with SARS-CoV-2 did not fully recover by six months. The proportion of individuals who had an infection who reported not having recovered decreased to 18.5% at 12 months and 17.2% at 24 months after infection. Consequently, the majority of patients who were ill after 12 months, were still ill after 24 months highlighting the absence of effective treatment [49]. On the other hand, three systematic reviews have been published recently that claim that exercise therapy is an effective treatment for long COVID. In this article, we analyzed those three systematic reviews, and the trials in it, to see if that conclusion is correct.

Systematic review number one

A systematic review by Torres et al. [11] concluded that "exercises can mitigate the effects of COVID-19 in each organ system that the virus affects" (p. 284 [11]). But also "that exercise should be considered a first-line strategy in the prevention and treatment of COVID-19 infection and long COVID disease" (p. 284 [11]). Yet this review did not include any exercise trials, instead it was a review of the literature and in large part it reviewed the literature on the benefits of exercise in healthy people which was then extrapolated to COVID-19 and long COVID patients. Torres et al. [11] acknowledged that by stating that "it should be noted that the evidence exists for nonCOVID-19 patients and needs to be verified in COVID-19 and long COVID patients" (p. 287 [11]) but ignored that in their conclusion. Additionally, this systematic review also ignored the presence of PESE/PEM in many patients who suffer from long COVID. Consequently, no evidence was presented that exercise is a safe and effective treatment for individuals who have long COVID and are suffering from PESE. Why the review didn't pay attention to PESE is unclear because as noted by for example, Décary et al. [50] in an editorial in the Journal of Orthopedic and Sports Physical Therapy (JOSPT) in April 2021, an online survey (n=3762 people living with long COVID), found that 89.1% of respondents experienced "worsening or relapse of symptoms after physical or mental activity during COVID-19 recovery" (p. 198 [50]). This is also known as PEM (Post-Exertional Malaise) or PESE (Post-Exertional Symptom Exacerbation) which "was most often triggered by physical activities and exercise" (p. 198 [50]). Additionally, "close to 75% of people living with long COVID still experienced PEM after 6 months" (p. 198 [50]).

This was also noted by Parker et al. [51] when they stated that, "Post-Exertional Symptom Exacerbation (PESE) or Post-Exertional Malaise (PEM), or a "crash" in layman's terms, has been reported as a characteristic symptom of PCS. PESE is defined as worsening symptoms following physical or mental exertion, typically 12-48h after activity and lasting days or (rarely) weeks. It is thought to involve an abnormal response following physical, cognitive, emotional, or orthostatic exertion, that would not have caused a problem before illness" (p. 2 [51]). Many doctors claim that deconditioning is the cause of PESE/PEM. This claim was investigated by Sørensen et al. [52] who used Cardiopulmonary Exercise Testing (CPET), which "has emerged as the preferred method to quantify the degree of exercise impairment" in 169 long COVID patients (p. 3 [52]). They "were advised to be physically active at as high an intensity level as possible and gradually return to usual sports activities" (p. 12 [52]). The "1-year follow-up results showed not statistically changes in any of the CPET parameters which correspond to a lack of improvement in self-reported physical fitness" (p. 12 [52]). Consequently, gradually increasing and returning to usual sport activities doesn't lead to improvement or recovery in long COVID. Just like it doesn't in ME/CFS.

Sørensen et al. [52] also noticed that "a considerable overlap between long COVID and ME/CFS has been increasingly recognized. The exercise intolerance reported in this study shares similarities with hemodynamic and gas exchange disturbances observed in patients with ME/CFS, suggesting the presence of common mechanisms" (p. 12 [52]). Moreover, as noted by Vieira Machado Ferreira and Oliveira, "the physical deconditioning theory does not explain the presence of persistent symptoms in patients who were affected by mild forms of the disease, many of whom did not even require hospitalization. Similarly, this theory does not explain the dissociation between the severity of hospitalization and the reduction in peak VO2 reported so far, nor does it explain the antagonism of the persistence of symptoms in patients with preserved peak VO2" (p. 3 [53]). But also, that "it is unacceptable to be simplistic when attempting to unravel the post-COVID-19 syndrome exercise intolerance mechanisms. More robust scientific evidence is needed before drawing simple conclusions" (p. 3 [53]). Finally, healthy people who are inactive, also known as healthy sedentary controls, do not suffer from worsening of symptoms after exercise. To the contrary, they improve physical function after resuming exercise training [35]. Exercise or exertional intolerance is not characteristic of PESE or PEM, yet symptom exacerbation disproportionate to the level of exercise in combination with an abnormally delayed recovery, is [50,52,54-56].

Systematic review number two

The second systematic review was one by Torres and Gradidge et al. [12]. They analyzed 32 studies, of which 22 were non-randomized studies without a control group. Torres and Gradidge concluded that "rehabilitation interventions significantly improved cardiorespiratory fitness and pulmonary function in post-COVID-19 infection patients" and that "rehabilitation interventions should be considered as a management tool for post-COVID-19 infection patients" (p. 6 [12]). Their recommendation for exercise therapy is partly based on the fact that "there was a significant difference in the 6-minute walk test… (51.69m)" (p. 1 [12]). In this article, we analyzed the 10 studies that did have a control group and we found that only three of them tested the efficacy of exercise therapy for long COVID. In the study by McNarry et al. [40] patients already had a normal VO2max score at baseline and 50.4% of participants dropped out or did not start the intervention [40]. This suggests that they didn't find the intervention helpful and/or acceptable. Only one of these three studies [39] used the six-minute walk test as an outcome measure. At baseline patients already walked 515m so that they already had fairly good fitness before starting treatment. Their improvement on the six-minute walk test of 65m (12.7%) could simply be down to the learning effect of repeating this test. Moreover, 39% of participants from the treatment group were lost to follow up which is suggestive that they didn't tolerate the treatment and/or didn't find it effective. None of the three studies investigated if patients were suffering from PESE/PEM. Additionally, the three long COVID studies in this review used badly designed control groups (no treatment/waiting list, control group) and as discussed earlier, this is known to artificially inflate a treatment effect.

On top of that the studies by Jimeno-Almazán et al. [33] and Li et al. [39] would have been excluded from the aforementioned homeopathy advice study for the EU, which included one of the main proponents of CBT and GET for ME, as there were only 19 and 59 participants in the treatment groups in those studies, respectively. Moreover, this systematic review noted that "most of the studies did not report adherence rate and adverse events" (p. 3 [12]). Yet one cannot conclude that a treatment is effective if one doesn't know if patients actually adhered to it. Also, the first, do no harm principle [57] is the main principle of medicine and one shouldn't recommend a treatment if one doesn't know if that treatment is safe or not. In conclusion, the studies in this second review do not provide any evidence that exercise treatment is a safe and effective treatment for long COVID patients who suffer from PEM/PESE.

Systematic review number three

The third systematic review was one by Sick & König [10] and included seven studies. Sick & König [10] concluded that "exercise enhanced aerobic fitness and physical function and relieved symptoms of dyspnea, fatigue and depression" in long COVID and that "the exercise programs were well tolerated with no adverse events" (p. 1 [10]). However, five of the seven studies were non-randomized studies without a control group. Four of these studies noted that one cannot come to a causal inference of efficacy in the absence of a control group. Yet all four of them continued to ignore this in their conclusion. Moreover, the two studies that did have a control group would have been excluded from the aforementioned homeopathy review for not having enough participants in the treatment group. Only one of the seven studies documented how many patients suffered from exertional intolerance but this non-randomized study without a control group, didn't specify if this was just exertional intolerance, or if patients suffered from PEM/PESE. Also, this study did not report the results for patients with and without exertional intolerance, separately. None of the studies in the systematic reviews investigated if patients suffered from PEM/PESE or not. More importantly, the systematic reviews itself did not investigate this either. This is despite the fact that the WHO recommends "excluding PESE before commencing exercise therapy" but also that "careful monitoring for PESE both during and after exercise, should be considered" (p. 119 [15]).

They also state that "in the absence of PESE, a cautious return to symptom-titrated physical exercise training" is recommended (p. 119 [15]). The studies and systematic review couldn't follow this advice because it was issued in the seventh version of the living guideline of clinical management of COVID-19 which was published in August 2023 when the systematic reviews were published as well. However, the WHO stated in the third version of the same guideline, which was published in November 2021, the following. "All rehabilitating patients should be educated about resuming everyday activities conservatively at an appropriate pace that is safe and manageable for energy levels within the limits of current symptoms and [they] should not be pushed for post-exertional fatigue" (p. 70 [9]). Additionally, the aforementioned study by Twomey et al. [3], which found that 58.7% of people with long COVID suffer from PEM, concluded in January 2022 that "PEM is a significant challenge for this patient group. Because of the potential for setbacks and deteriorated function following overexertion, fatigue and post exertional symptom exacerbation must be monitored and reported in clinical practice and in studies involving interventions for people with long COVID" (p. 1 [3]). Many health professionals think that post-exertional fatigue, i.e. tiredness after exercise, is PEM/PESE even though tiredness after exercise is simply a normal physiological response to exercise. This misunderstanding of PEM by many doctors is highlighted by the way the Dutch multidisciplinary guideline long-term complaints after COVID-19 (in Dutch: Richtlijn Langdurige klachten na COVID-19 [58]) defines it. The doctors in the committee that wrote the part in the guideline about the long-term complaints, consisted of five general practitioners, medical specialists (an internist, a chest physician, an ENT specialist, a geriatrician, a psychiatrist, a sports physician and a rehabilitation physician), an insurance physician, an occupational health physician, an epidemiologist and one of the leading ME/CFS specialists in the world. Normally the most knowledgeable doctors about a certain condition are part of a guideline committee. This committee defined PEM as excessive tiredness after exertion (in Dutch: "overmatige vermoeidheid na inspanning (post exertional malaise)" (p. 244 [58]) and they noticed that it is a frequently occurring problem. However, excessive tiredness after exertion is a normal physiological response when the intensity, duration and/or level of exertion are too much for the level of someone's fitness. PEM/PESE however, is something different and the following four elements are essential for its diagnosis:

a. a disproportional worsening of symptoms,

b. following trivial physical or mental exertion,

c. with loss of strength and/or loss of function,

d. and an abnormally delayed recovery.

PEM/PESE typically starts not immediately after exertion, but hours later. Often, it also starts the next day and it can last for hours, days, weeks or even months. If someone goes too far over one's limit, then the result is a relapse with permanent loss of function because in the absence of effective pharmacological treatment, one will not recover from that. The systematic review by Sick & König [10] stated that "before prescribing a training program to PCS patients, a thorough screening for exercise intolerance in form of PEM is recommended" because "relapses triggered by exercise have been identified as a frequent symptom in PCS cases" (p. 8 [10]). Yet, they do not make it clear why they didn't do a thorough screening for this in the studies in their review. Sick & König [10] also state that "patients affected by PEM or who were diagnosed with ME/CFS should not be exposed to conventional exercise programs, as it is potentially harmful for this population. A pacing protocol with incremental phases of physical activity according to RPE scores could be a beneficial alternative" (p. 8 [10]). Their reference to that is a longitudinal prospective cohort study by Parker et al. [51] of individuals with PCS that used the WHO Borg CR-10 pacing protocol with five incremental phases of activity. Phase 1 was the "Preparation for return to exercise" which consisted of "Controlled breathing exercises, Gentle stretching & balance exercises and Gentle walking" (p. 2 [51]). Phase 4, for example, consisted of "High-intensity exercises, Running, Cycling, Swimming and Dancing" and in phase 5, "patients should be able to complete pre-COVID-19 activities" (p. 2 [51]). The guidance advises the individual "to stay at each phase for a minimum of 7 days" (p. 3 [51]).

The study concluded that "the WHO Borg CR-10…structured pacing protocol…substantially reduced PESE episodes whilst increasing activity levels even in a cohort of individuals with long-standing PCS symptoms" (p. 9 [51]) and that "the results are impressive" (p. 9 [51]). However, the study itself noted that the small sample size (n=31) was one of the limitations of their study. Moreover, it was a non-randomized study without a control group. Consequently, it's impossible to make any causal inference. Why this was ignored by Parker et al. [51], but also by the systematic review by Sick & König [10], is unclear. Parker et al. [51] also states that there is "a body of existing literature [that] explores PESE within Myalgic Encephalomyelitis (ME) or Chronic Fatigue Syndrome (CFS), but little is known about PESE within PCS patients. Research exploring physical activity progression and PESE in people with PCS has not reported symptom exacerbation in response to exertion" (p. 2 [51]). The research they refer to are studies by Halle et al. [59], Daynes et al. [60] & Putrino et al. [61]. However, Halle et al. [59] do not mention or discuss PCS, or PESE in PCS. Daynes et al. [60] was a small (n=32) non-randomized, non-blinded study without a control group. The authors themselves acknowledge that the "sample size is small and there is no comparator group" (p. 3,4 [60]). But again, these authors go on to ignore this when they conclude that "COVID-19 rehabilitation appears feasible and significantly improves clinical outcomes" (p. 2 [60]).

The third study that Parker et al. [51] used, was a study by Putrino et al. [61] which is a pre-print from 2021, which is available on Research Square but hasn't gone through peer review. Why this is not mentioned by Parker et al. [51] is unclear. Putrino et al. [61] investigated the efficacy of Autonomic Conditioning Therapy (ACT) for Post-Acute COVID-19 Syndrome (PACS) which used "principles of graded submaximal aerobic exercise" (p. 8 [61]). The authors conclude that "this is the first intervention reported to successfully demonstrate a reduction in fatigue, the most common and debilitating symptom, in individuals with PACS" (p. 8 [61]). However, the authors acknowledge that "this study has limitations inherent to its non-randomized, retrospective design" and that patients might have been "self-selected" (p. 9 [61]). As noted by Alarie & Lupien [62], "self-selection bias leads to non-generalizable results" because participants are not representative of the population under investigation (p. 1 [62]). This is of particular importance because only 40% of participants who consented to take part in the study by Putrino et al. [61], actually took part. This also suggests that 60% did not think that exercise therapy was the right treatment for them and/or they thought it was not safe for them to follow such a program. Consequently, this study which didn't go through peer review, was another non-randomized, non-blinded small study (n=31) without a control group, which makes it impossible to make any causal inference of efficacy of the treatment under investigation.

In conclusion, the studies by Halle et al. [59], Daynes et al. [60] & Putrino et al. [61] do not provide any evidence that physical activity progression does not lead to symptom exacerbation and PESE in response to exertion in people with PCS. Nor do these studies provide any evidence that this treatment is effective. In addition, an exercise program with incremental increases of activity is not what pacing is about [63]. Instead, it is Graded Exercise Therapy (GET) which has been relabeled into pacing. But relabeling a horse into a frog, doesn't make a horse a frog. Unless of course you don't know what, a horse is. As noted by psychologist Goudsmit, the developer of pacing for ME/CFS, "pacing is not a type of treatment or therapy. It is simply a way of managing energy" (p. 4 [63]) whereby patients try to stay within their limits to try to reduce "the number and severity of [symptom exacerbations and] relapses" (p. 4,5 [63]). Additionally, the two studies in this review that did have a control group [33,34], used badly designed control groups (no treatment) and as discussed earlier, this is known to artificially inflate a treatment effect. Moreover, the treatment groups in these two studies were very small, with only 19 and 20 participants respectively, in it. In conclusion, the studies in this third review do not provide any evidence that exercise treatment is a safe and effective treatment for long COVID patients who suffer from PEM/PESE.

Graded exercise therapy for cardiovascular autonomic dysfunction in PCS

According to a systematic review by Fedorowski et al. [64], "Cardiovascular Autonomic Dysfunction (CVAD) is a malfunction of the cardiovascular system caused by deranged autonomic control of circulatory homeostasis. CVAD is an important component of post-COVID-19 syndrome, also termed long COVID" (p. 1 [64]). The management of CVAD in post-COVID-19 syndrome should involve both pharmacological and non-pharmacological methods. According to Fedorowski et al. [64], "especially effective" are an "exercise training program…and compression garments" (p. 2 [64]). They also state that the "application of graded exercise therapy is especially important in the setting of coexistent ME/CFS to reduce the effects of the highly expected post-exertional malaise" and their reference for that is the PACE trial by White et al. (p. 11 [65]). The PACE trial is the largest trial of CBT and GET for ME/CFS, that has so far been conducted, with 160 patients in each of the four treatment groups. First, according to the final version of the PACE trial protocol, PEM was defined as "feeling ill after exertion" (p. 156 [66]) which as discussed earlier, is not what PEM is. Second, White et al. [65] concluded that their treatments were effective, yet their results didn't show that. For example, according to both primary outcomes, fatigue and physical functioning, patients were still ill enough to re-enter the PACE trial again and be treated with GET again after treatment deemed effective by Fedorowski et al. [64] and the trial itself, as can be seen in Table 4. Moreover, GET did not lead to an improvement in CFS symptom count [65] or an improvement in quality-of-life scores and it had a negative instead of a positive effect on employment and illness benefit status [67]. Additionally, fitness did not improve either. Even though, if the application of GET would have reduced the effects of the highly expected post-exertional malaise, as stated by Fedorowski et al. [64], then fitness should have improved substantially after six months of exercising five days a week.

In a reply to van Rhijn-Brouwer et al. [68], who concluded that GET should not be recommended for patients with post-exertional malaise (p. 1 [68]), Fedorowski et al. [69] claimed about the efficacy of GET, that "the jury is still out; we should wait for the verdict and respect it when it comes" (p. 1 [69]). Yet as can be seen in Table 4, both primary outcomes of the PACE trial (fatigue and physical functioning) clearly show that patients remain severely disabled after treatment deemed to be effective by the PACE trial [65] and by Fedorowski et al. [64] Consequently, the jury has already spoken. This confirms the conclusion by the British National Institute for Health and Clinical Excellence (NICE) in its updated ME/CFS guidelines published in October 2021, in which it concluded that GET doesn't lead to improvement or recovery in ME/CFS [70, 71], just like patients have been saying for decades. The Magenta trial by Gaunt et al. [72] (n=241), which was published in March 2024, concluded that "there was no evidence that GET was more effective… than AM [Activity Management] with very limited improvement in either study group evident by the 6-month or 12-month assessment points" (p. 1 [72]). Moreover, Gaunt et al. [72] concluded that the accelerometer data suggest that "the MAGENTA participants had a reduction in moderate-to-vigorous-intensity physical activity at 3 and 6 months" (p. 7 [72]). This shows that GET had a negative effect on fitness and it is suggestive that GET was harmful.

Table 4: Fatigue and physical functioning scores after treatment with GET in the PACE trial [65].

Fatigue and Physical Functioning Scores	24 Weeks (End of Treatment)	52 Weeks (6 Months Follow-up)
Fatigue score after GET	21.7	20.6
Fatigue entry requirement	18 or more	18 or more
No fatigue	9 or less	9 or less
Physical functioning score after GET	55.4	57.7
Physical functioning score entry requirement	65 or less	65 or less
Abnormal level of physical function according to the PACE trial recovery article	65 or less	65 or less
Severely disabled	70 or less	70 or less
Ability to do all activities	A score of 100	A score of 100

A fatigue score of nine or less represents no fatigue according to review by Jackson [73]; A physical functioning score of 65 or less represents an "abnormal level of physical function" according to the PACE trial recovery article [74]; A physical functioning score of 70 or less represents severely disabled according to Tummers et al. [75] which included two of the leading proponents of the cognitive behavioral model for ME/CFS (Bleijenberg and Knoop); a physical functioning score of 100 represents the "ability to do all activities" according to Van Geelen et al. [76], which included a leading pediatric proponent of the cognitive behavioral model for ME/CFS (van de Putte).

Employment and illness benefit status

The economic costs of Long COVID disabling a previously productive workforce are significant. For example, estimates place the total US economic cost of PASC to "range from US$140 to US$600 billion annually" (p. 1 [77]). Hence, effective treatments are urgently needed. Ostrowska et al. [16], one of the non-randomized studies without a control group in the systematic review by Sick & König [10], noted that "due to the growing number of patients with long COVID-19, there is an urgent need to create safe and effective rehabilitation programs to relieve symptoms and promote early return to work and social roles" (p. 8 [16]). Smith et al. [19] another study in that review, noted that 406 participants were employed at baseline (67.9%) yet 137 of them (22.9%) were unable to work due to long COVID. Yet employment status was not an outcome measure of both studies. It is unclear why this was the case. On top of that, none of the other studies into the efficacy of exercise treatment for long COVID used work and illness benefit status as an outcome measure. An extensive review of the literature on the other hand showed that GET had a negative, instead of a positive effect on work and illness benefit status in ME/CFS in clinical trials and in the official ME/CFS clinics in Belgium and the UK [78].

Safety

According to the systematic review by Sick & König [10] "the exercise programs were well tolerated with no adverse events" (p. 1 [10]). The systematic review by Torres & Gradidge et al. [12] didn't report on safety. Additionally, both reviews did not investigate if there were patients in the studies who suffered from PEM/PESE, even though that would be essential to know if the treatments would be well tolerated with no adverse events, because patients who suffer from PEM/PESE would be the ones who would be negatively affected or harmed by exercise treatments. Consequently, Sick & König [10] should have concluded that it is unclear if exercise programs were well tolerated by patients who suffer from PEM/PESE because studies did not investigate that. In an interview on Dutch TV, pediatrician Terheggen-Lagro and medical psychologist Oostrom from the Amsterdam UMC (University Medical Centre), a leading hospital in the Netherlands, stated that they started to treat children with long COVID with CBT as designed for ME/CFS, which contains an element of GET, and GET. However, they noted that instead of helping patients recover, it made them worse, just like in ME/CFS. Consequently, they stopped using these treatments [79].

As mentioned before, NICE published its updated ME/CFS guidelines in October 2021 [70]. As part of that review process, it commissioned the Oxford Brookes University to carry out a survey amongst ME/CFS patients (n=2274) on the safety of CBT and GET. In their report which was published in February 2019 [80], the Oxford Brookes University reported the following: 98.5% of the patients who took part in the survey experienced post-exertional malaise, the core symptom of the disease. Worsening of symptoms after GET was reported by 81.1% and the percentage of severely affected patients increased from 12.9% to 35.3%. It's not surprising that gradually increasing exercise is harmful because there are many studies documenting the negative effect of exercise/GET for patients with ME/CFS [71,80-82]. Many long COVID patients have reported the same response to exercise, which is not surprising in patients who are suffering from PEM/PESE as well. A recent study by Appelman et al. [83] which used muscle biopsies to examine the effect of exercise in patients with long COVID, found that "muscle abnormalities worsen after post exertional malaise in long COVID" (p. 1 [83]). It was a patient-led initiative that introduced the name long COVID and brought it to the attention of the medical profession [4]. It's now a patient-led initiative that is not only raising awareness about long COVID with a song, but also about the dangers of exercise therapy for patients with long COVID who suffer from PEM/PESE [84]. Our analysis has highlighted the dangers of a gradual increase in activity for those patients yet exercise trials do not take that into account. This might reflect a lack of knowledge about this by the medical profession. The following lines from that song highlight this.

Doctors might also say

you need to push

through your symptoms

would be nice

if that was right

would be nice

if that was right

it makes it worse

it makes it worse

it only

makes it worse

Supportive therapy that may enhance patient outcomes in long COVID

In addition to the concerns surrounding exercise therapy, it is important to consider the potential role of supplementary treatments that may alleviate some symptoms of long COVID. For instance, the administration of melatonin has been shown to improve several physiological and mental health parameters, which are often compromised in long COVID patients. According to a review on melatonin supplementation [85], nighttime melatonin administration can modulate the circadian components of the sleep-wake cycle, enhance sleep efficiency, improve mood status, and reduce inflammatory markers and oxidative stress. These benefits suggest that melatonin could be a valuable part of a multi-faceted treatment approach for long COVID, particularly for patients experiencing disruptions in sleep and circadian rhythms. Moreover, according to some research, Melatonin possesses antiviral function and alleviates oxidative stress in many inflammatory diseases. It might well be that by supplementing diets with Melatonin, it will not only modulate sirtuin Signaling Pathways (SIRT1) in the immune system, to counteract the cytokine storm and oxidative stress, the root causes of severe inflammation and symptoms in patients with COVID-19 [86-89]. But it might also have some effect on alleviating some of the long COVID symptoms as research by Peluso et al. [90] found tissue T cell activation and viral persistence for up to 2 years following initial COVID-19 illness in long COVID patients. This suggests that tissue viral persistence could be associated with long-term immunological perturbations.

Recommendations for the design of high-quality treatment studies

There are no effective treatments for the 400 million people with long COVID according to a conservative estimation [91] and the estimated 17 to 24 million people with ME/CFS [92]. Consequently, there is an urgent need to find causative treatment approaches for more than 400 million people with post infectious diseases [93]. In this analysis we have highlighted the many problems with exercise studies for long COVID. A healthy lifestyle incorporating exercises is important for everybody, however, long COVID patients who suffer from PEM/PESE are unable to exercise their way out of PEM/PESE. Consequently, GET with fixed incremental increases in exercise or any other form of gradually increasing exercise will lead to flare ups and relapses, which has implications for future research. Requirements for high-quality treatment studies, which will enable us to find effective treatments for long COVID, are the following.

A. Studies should investigate how many patients suffer from PEM/PESE and they should be excluded from exercise studies;

B. Other studies should report results separately for those with and those without PEM/PESE;

C. There need to be at least 75 participants in the treatment group and a similar number in the control group unless it's a phase one, feasibility or observational study or a case report to reduce the chances that improvements are simply down to chance;

D. Non-blinded studies like exercise studies should use objective primary outcomes (i.e. step test, six-minute walk test or the actometer, as discussed earlier) alone or in combination with a subjective one which is relevant to patients like quality-of-life scores;

E. Studies should also use work status/number of hours worked and benefit status, as an objective outcome measure;

F. Control groups should be properly matched and designed and everything in the control group should be the same as in the treatment group, including expectations raised by the therapist about the efficacy of the treatment, apart from the treatment received;

G. Studies should not use a badly designed control group (wait list, no treatment, usual care or specialist medical care)

H. A non-randomized study without a control group should not be conducted, unless it's a case report or an evaluation study;

I. The study protocol should be published before the start of the study;

J. Non-blinded studies that deem treatments to be effective, based on subjective outcomes, even more so if there is no control group, should be rejected for publication;

K. Misdiagnosed patients should be removed from a study and its analysis;

L. Adherence rate to treatment should be reported;

M. Dropout rate should be reported;

N. Harm should be reported;

O. Patients and/or carers should be involved in the design and conduct of these studies;

P. Studies should also be conducted about the severely ill long COVID patients, i.e. those who are bedbound;

Q. Studies that resort to selective reporting of objective outcomes should be rejected by journals;

R. Studies that make extensive outpoint changes, use a post hoc definition of recovery, have an overlap in entry and recovery criteria, label the severely ill as recovered, et cetera, should also be rejected by journals.

Conclusion

In this article, we reviewed the evidence from three systematic reviews, that all concluded that exercise is an effective treatment for long COVID. Our review shows that there were a number of important issues with the three systematic reviews. The first systematic review was a review of the literature which investigated the benefits of exercise in healthy people. The benefits were then extrapolated to COVID-19 and long COVID patients even though one can only say something about the efficacy of a treatment for a particular condition if that treatment is actually investigated for that particular condition. The second systematic review included 32 exercise studies, 22 of those did not have a control group and only 3 of the remaining 10 investigated exercise therapy for long COVID. The third systematic review included seven exercise studies for long COVID, yet, five of them did not have a control group. Consequently, any causal inference about the efficacy of a treatment is impossible because of that. The treatment groups in the remaining five studies from both systematic reviews were all small to very small. Additionally, these five studies used a badly designed control group. The proportion of patients with PEM or PESE was not described by the studies or the systematic reviews, and none of the trials described the severity of PEM/PESE. It is unclear why they didn't do that because the potentially harmful effects of exercise therapy for patients who suffer from PEM/PESE has been documented by many studies including the Living Guidance for Clinical Management of COVID-19 by the WHO. Gradually increasing exercise is not an effective treatment for PESE/PEM, instead it is a diagnostic test, albeit, a very harmful one which in the absence of effective pharmacological treatments, can render people bedridden for life. Consequently, patients who do suffer from PEM/PESE cannot do it, and patients who can do it, have been wrongly diagnosed with PEM/PESE. In summary, the three systematic reviews do not provide any evidence that exercise therapy is a safe and effective treatment for long COVID patients who suffer from PEM/PESE. Additionally, the medical profession potentially increases the risks for the health of long COVID patients who suffer from PEM/PESE, by not excluding those patients from exercise trials.

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