Effect of Physical Exercise–Based Rehabilitation on Long COVID: A Systematic Review and Meta-analysis

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ABSTRACT

ZHENG, C., X.-K. CHEN, C. H.-P. SIT, X. LIANG, M.-H. LI, A. C.-H. MA, and S. H.-S. WONG. Effect of Physical Exercise–Based Rehabilitation on Long COVID: A Systematic Review and Meta-analysis. *Med. Sci. Sports Exerc.*, Vol. 56, No. 1, pp. 143–154, 2024. **Purpose:** The number of persons living with post–coronavirus disease 2019 (COVID-19) conditions or long COVID continues to rise worldwide; however, the etiology and the treatment of long COVID remain nebulous. Therefore, efficient, feasible, and cost-effective therapeutic strategies for a large population with long COVID remain warranted. Physical exercise–based rehabilitation is a promising strategy for long COVID, although its therapeutic effects remain to be determined. This systematic review and meta-analysis aimed to examine the effects of physical exercise–based rehabilitation on long COVID. **Methods:** The electronic databases Medline, Embase, Global Health (Ovid), CINAHL (EBSCO), Web of Science, WHO Global Research Database on COVID-19, LitCovid, and Google Scholar were searched from their inception to November 2022. The identified articles were independently screened by three reviewers, and a random-effects model was used to determine the mean differences in the meta-analysis. **Results:** Twenty-three studies involving 1579 individuals who had COVID-19 (752 women) were included. Physical exercise–based rehabilitation showed beneficial effects on long COVID-related symptoms characterized by dyspnea, fatigue, and depression, as well as on the 6-min walk test, forced expiratory volume in 1 s/forced vital capacity, and quality of life in people who had COVID-19. **Conclusions:** Physical exercise–based rehabilitation is a potential therapeutic strategy against long COVID and can be applied as a routine clinical practice in people who have recovered from COVID-19. However, customized physical exercise–based rehabilitation programs and their effects on specific types of long COVID require future large-scale studies. **Key Words:** PHYSICAL EXERCISE, LONG COVID, REHABILITATION, COVID-19, SEQUELAE, 6-MWT

The effectiveness of vaccination strategies, the improvement in population immunity, and the predominance of less harmful severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) variants have resulted in the mildest presentation of acute coronavirus disease 2019 (COVID-19) to date. However, it remains a considerable public health threat owing to the hyper-transmissibility of currently dominant variants and the rapid increase in the number of individuals with post-COVID-19 conditions (also known as long COVID) (1,2). Currently, the prevalence of long COVID was estimated to be approximately 50% among individuals with COVID-19 at 4 months postinfection; this is increasing over time as long COVID can last for months or years as reported in a systematic review of global data (3). By contrast, the World Health Organization (WHO) estimates the prevalence to be around 10%–20% of all the people who have recovered from COVID-19 (4). This discrepancy in the prevalence of long COVID between different reports can be attributed to the varied definitions of long COVID and populations used. Advanced age, overweight/obesity, poor prepandemic general health, Asian ethnicity, female sex, greater severity of COVID-19, ancestral variants of SARS-CoV-2, and reinfection are factors that determine the prevalence, duration, and severity of long COVID (5–9). Although COVID-19 vaccination is currently the only preventive measure for long COVID and it has some favorable effects, vaccination can only provide partial protection against long COVID (10). Moreover, the effects of COVID-19 drugs or other relevant treatments on long COVID

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remain largely unknown and require further clinical assessments (11). The clinical manifestations of long COVID are highly complex and widespread, primarily comprising fatigue, "brain fog" (cognitive impairment), dyspnea, persistent cough, chest pain, muscle aches, and mental disorders (3,12). Therefore, various guidelines have been established for the management of long COVID, wherein self-management and multidisciplinary rehabilitation are generally recommended owing to the persistence and heterogeneity of long COVID and the lack of effective treatments (13,14). Regarding multidisciplinary rehabilitation, physical exercise–based rehabilitation has shown potential as a promising therapy against long COVID, although its effects may be symptom dependent. Nevertheless, the effectiveness of physical exercise–based rehabilitation strategies for long COVID remains inconclusive owing to limited evidence and varied criteria of patients with long COVID in previous studies.

Physical exercise has long been used in the rehabilitation of multiple postdisease conditions, such as cardiopulmonary sequelae, cancer or cancer therapy-related complications, and mental disorders (15–17). It is not only known for its general health benefits, cost-efficiency, and accessibility but also for its diverse therapeutic effects that act as a "polypill" on various organs or tissues in patients (18). Thus, physical exercise–based treatment is desirable for the rehabilitation of persistent sequelae with heterogeneous manifestations, including long COVID. Emerging evidence indicates that physical exercise–based inpatient and outpatient rehabilitation is beneficial for people who have had COVID-19, as it mitigates the symptoms and sequelae of COVID-19 in both acute and postacute phases (19–21). However, most of these pioneering studies focused on the pulmonary or locomotor symptoms of long COVID; thus, the effectiveness of physical exercise–based rehabilitation for long COVID with symptoms other than pulmonary or locomotor impairments remains unclear. On the contrary, novel concerns regarding the detrimental effect of resuming physical exercise or activities shortly after recovery from COVID-19 have also been raised. A cross-sectional study indicated that physical activities worsened the symptoms of long COVID in the majority of adults with post-COVID conditions (74.84% of the responders) (22). In particular, the inappropriate resumption of physical activities or exercise shortly after infection is unsafe for people who had severe COVID-19 illness (23). More importantly, a large international cohort study revealed that physical exercise is one of the main triggers of relapsing symptoms in individuals with long COVID (24). Despite well-established guidelines for resuming physical exercise postinfection for asymptomatic patients with COVID-19, these guidelines may not be suitable for persons with long COVID (25,26). Therefore, guidelines for supervised physical exercise–based rehabilitation programs for the prevention or alleviation of long COVID are urgently needed.

To the best of our knowledge, the effect of physical exercise–based rehabilitation on long COVID has not been examined in a systematic review and meta-analysis, although many narrative reviews have proposed and discussed the potential benefits and drawbacks of physical exercise–based rehabilitation with respect to long COVID (27–29). Two systematic reviews have examined the effect of pulmonary rehabilitation on sequelae of COVID-19, primarily focusing on "breathing exercises" for respiratory muscle training (30,31). However, a small number of articles were identified in their systematic search, and the criteria for sequelae of COVID-19 in the included studies did not meet the definition of post-COVID-19 conditions or long COVID established by the WHO (1). In this context, the effect of physical exercise–based rehabilitation on long COVID remains unclear; therefore, the aim of the present systematic review was to synthesize published studies that focused on the effects of physical exercise–based rehabilitation on long COVID.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (32) and was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022327778).

Search strategy. The following electronic databases were systematically searched from inception to November 13, 2022, to identify the relevant articles regarding the effect of physical exercise–based rehabilitation on long COVID: Medline, Embase, Global Health (Ovid), CINAHL (EBSCO), and Web of science. Additionally, we also searched the WHO Global Research Database on COVID-19, LitCovid, Google Scholar (the first 500 titles, as previously described [33]), and the reference lists of all included studies to identify relevant articles. Identified articles from the electronic database were imported into EndNote reference management software, and duplicates were removed before further screening. Full search items used in the various databases are presented in Supplemental Table 1, Supplemental Digital Content (http://links.lww.com/MSS/C932).

Eligibility criteria. Titles and abstracts of all identified records were screened by three independent reviewers (C.Z., X.C., and X.L.) to exclude irrelevant articles, after which a full-text screening was conducted by the same reviewers. Any disagreement was resolved by discussion or a fourth reviewer (S.W.). The following studies were considered eligible for inclusion in our systematic review: 1) peer-reviewed original studies (excluding case reports); 2) articles written in English; 3) articles with full text available; 4) studies in which the participants were adults who had recovered from confirmed acute COVID-19; 5) studies in which the main outcomes were potential symptoms of long COVID classified according to WHO guidelines (1), in which physiological and pathological parameters were measured or reported within at least 3 months after COVID-19 and could not be explained by an alternative diagnosis; and 6) studies in which physical exercise was the main strategy in the rehabilitation program for individuals with long COVID. The assessment time could be either before or after the intervention because the rehabilitation was performed

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shortly after discharge from hospital (<3 months postinfection) in some cases. For those articles that did not directly report the duration between the infection and the long COVID symptom assessment, the duration was calculated or estimated based on the information related to time in the articles, such as length of hospital stay, duration from discharge to enrollment, intervention duration, and/or duration from discharge to long COVID symptom assessment. Authors of original articles were contacted if the relevant information was incomplete or unclear. Studies were excluded if information about the duration between the infection and the long COVID symptom assessment was inaccessible or if the duration was less than 3 months. For articles published before the release of the WHO's definition of long COVID, we evaluated them using the same criteria (assessment time ≥3 months postinfection).

Data extraction. Study data were extracted by two independent reviewers (C.Z. and X.L.), and discrepancies were resolved by discussion with a third reviewer (X.C.) until a consensus was reached. The following information or data of study characteristics were extracted using a standardized data extraction form (34) if it was reported in the original articles: bibliographic details (author, year, and country), participant characteristics (sample size, sex, and age), physical exercise–based rehabilitation (type, intensity, frequency, and duration), main outcomes (long COVID-related physiological and pathological parameters, such as 6-min walk test [6-MWT], dyspnea, and fatigue), adverse effects of physical exercise–based rehabilitation, and key findings or conclusion of the study. In addition, the mean and the SD of the main outcomes measured before and after physical exercise–based rehabilitation were extracted for the pooled-effects analysis. For missing data, the corresponding author of the study was contacted for the original data, or data in available graphs were extracted using WebPlotDigitizer (35).

Study quality. The risk of bias in each included study was assessed by two independent reviewers (X.L. and M.L.) using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (36) and the Newcastle–Ottawa scale (37) for randomized controlled trials (RCT) and nonrandomized studies, respectively. Discrepancies regarding quality ratings were resolved by discussion between two reviewers (X.L. and M.L.) or with a third reviewer (C.Z.) until a consensus was reached.

Meta-analysis. A meta-analysis was conducted to assess the effects of physical exercise–based rehabilitation on specific long COVID-related outcomes using the Comprehensive Meta-Analysis Software 2.0 if the targeted outcome measures were reported by at least three studies. Random-effects models were used to analyze the pooled effects estimated based on the effects of physical exercise–based rehabilitation in studies with different types of designs, including RCT, controlled clinical trials (CCT), and one-group pretest–posttest design studies. The mean differences (MD) or standardized mean differences (SMD) with 95% confidence intervals (CI) were used according to whether the outcomes measurement was undertaken in the same or different ways. Heterogeneity was evaluated using Higgins's I^2 test (38). The I^2 value was applied to determine the level of study heterogeneity, including low ($I^2 \leq 25\%$), moderate ($I^2 > 25\%$ and $I^2 \leq 50\%$), substantial ($I^2 > 50\%$ and $I^2 < 75\%$), and high ($I^2 \geq 75\%$) heterogeneity. Graphs were plotted using Prism GraphPad software. A P value <0.05 was considered statistically significant.

RESULTS

Article selection. Systematic and manual searches in the electronic databases yielded 14,106 articles. After excluding duplicates, the titles and abstracts of 9342 articles were screened. Finally, 23 articles (19 from full-text screening and 4 from the reference list search) (19,20,39–59) met the inclusion criteria following the full-text screening of 464 articles, of which 21 were included in the meta-analysis and 2 were excluded owing to data unavailability (46,58) (Fig. 1).

Quality assessment. The risk of bias of each study included in this systematic review was assessed using the RoB 2 and Newcastle–Ottawa scales for the RCT and CCT or one-group pretest–posttest design studies, respectively (Supplemental Tables 2 and 3, Supplemental Digital Content, http://links.lww.com/MSS/C932). There were concerns regarding seven RCT (41–44,46,48,51), and three had low risk (45,50,52). In addition, the quality score of 13 included studies (19,20,39,40,47,49,53–59) ranged from 5 to 9, which represented a moderate risk of bias. Publication bias was not evaluated in this systematic review, as no outcome was reported in over 10 studies.

Study characteristics. Overall, 1579 individuals who had COVID-19 (827 men and 752 women) 18–84 yr old were included in the study, most of which (1269 of 1579) were hospitalized patients with COVID-19; five studies did not provide information regarding hospitalization (39,43,46,48,52) (Supplemental Tables 4 and 5, Supplemental Digital Contents, http://links.lww.com/MSS/C932). A total of 11 studies had a one-group pretest–posttest design (19,20,39,40,49,53–57,59), whereas 12 were either RCT or CCT (41–48,50–52,58). The frequent use of the one-group pretest–posttest design can be attributed to the urgent need for patients who experienced severe COVID-19 disease and the lack of standardized treatment for the patients allocated to the control group. Additionally, most studies were published in the previous 2 yr and set in European countries (11 of 23), namely, Spain (48,49), Italy (53), the United Kingdom (19), Belgium (55,58), Austria (20), France (52), Poland (57), and Greece (40,56). Other studies were conducted in Brazil (3 of 23) (41,44,46), China (2 of 23) (47,51), the United States (2 of 23) (45,59), Saudi Arabia (1 of 23) (39), Australia (1 of 23) (50), Chile (1 of 23) (54), Iran (1 of 23) (42), and India (1 of 23) (43).

Physical exercise–based rehabilitation was the intervention used for long COVID in the included studies. Rehabilitation was provided to patients who had recovered from COVID-19 two to five times a week for 2–12 wk. All studies used a mixed type of physical exercise as the intervention, which primarily included aerobic or endurance training (19,20,39–41,44,45,48–55,58,59), resistance or strength training (19,20,39–41,44,45,48,50,51,53–59), stretching or flexibility training (40,45,54), and motor or balance

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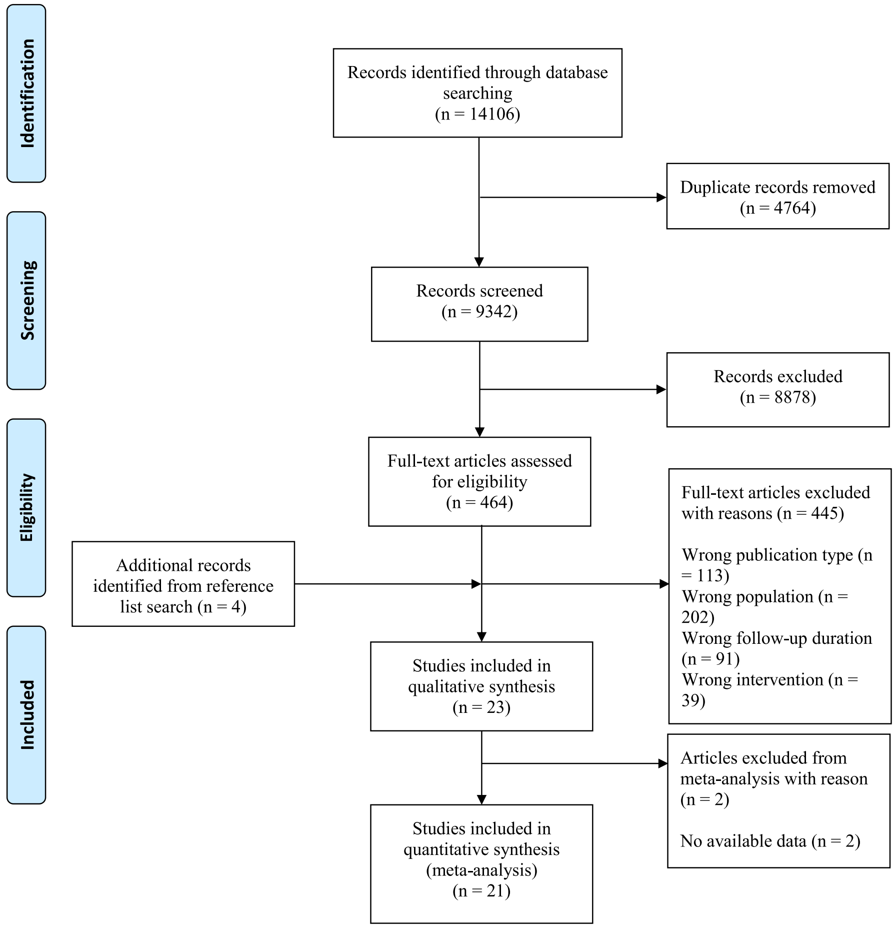

FIGURE 1—Flowchart of publications included in the systematic review and meta-analysis (PRISMA diagram). PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

training (45,49,56). In addition to conventional physical exercise, yoga (43), Pilates (42), and interval training (46,47,57) were also used. Light- to moderate-intensity exercise (e.g., aerobic exercise) was applied in almost all physical exercise–based rehabilitation programs, except in two studies in which relatively high-intensity exercise training was also included (39,47). Notably, unlike conventional physical exercise–based rehabilitation, respiratory muscle exercise was used alongside other types of physical exercise in some of the studies (20,47,51,59). In addition to physical exercise, other rehabilitation strategies such as educational discussion and fatigue management were introduced to people who had had COVID-19 in some studies (19,49), although physical exercise remained the primary rehabilitation strategy.

Long COVID-related outcomes were assessed at least 3 months after infection, although the implementation of physical exercise–based rehabilitation, such as inpatient rehabilitation, may have started before the assessments (41,42,45–47,54–57,59). Although many symptoms of long COVID were noted in the included studies, only a few, mainly those related to cardiopulmonary and locomotor functions, were assessed before and after physical exercise–based rehabilitation using different tests. Pulmonary function tests included assessments of forced vital capacity (FVC), forced expiratory volume during 1 s (FEV_1), FEV1/FVC, peak expiratory flow, maximum inspiratory pressure (MIP), maximal expiratory pressure, respiratory exchange ratio, transfer factor of the lung for carbon monoxide (TLCO or DLCO), and maximum voluntary ventilation (19,20,40–42,44,48,49,51,53,55,57).

Physical exercise or locomotion-related tests included the maximal oxygen consumption ($\dot{V}O_{2max}$), 6-MWT, sit-to-stand test (STST), short physical performance test, handgrip strength, lower limb muscle strength, muscle quantity, motor-functional independence measures, incremental shuttle walking test, and maximal workload measurement (19,20,39–41,44–51,53–56,58,59). In addition, psychological and psychiatric functions, such as cognitive function (19,49,55,59), anxiety, and depression (19,43,44,48,49,55,56,59), dyspnea (20,40,44,45,48,51,52,54,56,57,59), fatigue (19,20,40,44,48–50,56,57), quality of life (QoL) (19,20,39,42,43,48–52,56,59), kinesiophobia and sarcopenia in older adults (39), sleep quality (40), blood pressure (40), and immune or hematological parameters (46,47), were also determined in some of the included studies.

For adverse events, the majority of included reported no adverse event observed during physical exercise–based rehabilitation (19,20,41,43,48,50,56,58), whereas 12 included studies did not report adverse event (39,40,42,44,46,47,49,52–55,57). Importantly, a major adverse event was reported by a person who had been attended in-person rehabilitation after recovery from COVID-19 in an included study (59). In addition, minor adverse events, such as muscle strain, weakness, cough, dizziness, chest pain, and back pain, were reported by in a small number of studies (45,51).

Meta-analysis. Because COVID-19 was initially classified as a respiratory disease, pulmonary function tests were the most common outcome evaluated in the included studies. FEV1 (SMD = 0.37, 95% CI = 0.00 to 0.75, I^2 = 47% versus SMD = 0.15, 95% CI = −0.02 to 0.33, I^2 = 58%) and FEV1/FVC (MD = 3.41, 95% CI = 1.05 to 5.76, I^2 = 58% versus MD = 0.23, 95% CI = −1.64 to 2.10, I^2 = 58%) were significantly improved by physical exercise–based rehabilitation in RCT/CCT, but they remained unchanged in the pretest–posttest design studies (Fig. 2). Conversely, no significant changes in FVC were observed in either the RCT/CCT (SMD = 0.04, 95% CI = −0.22 to 0.30, I^2 = 0%) or the pretest–posttest design studies (SMD = 0.07, 95% CI = −0.05 to 0.19, I^2 = 13%) (Supplemental Fig. 1, Supplemental Digital Content, Pooled analysis on the effect of physical exercise–based rehabilitation on FVC, MIP, TLCO/DLCO, http://links.lww.com/MSS/C932). In addition, MIP (SMD = 0.77, 95% CI = 0.56–0.98, I^2 = 0%) and TLCO/DLCO (SMD = 0.31, 95% CI = 0.04–0.58, I^2 = 22%) were significantly increased after physical exercise–based rehabilitation in the pretest–posttest design studies

A

FEV1

Study	Standardized Mean Difference	(95%CI)	Weight (%)
RCT or CCT			
Campos et al., 2022	0.01	(-0.67, 0.70)	16.54
Amaral et al., 2022	0.12	(-0.59, 0.84)	15.74
Li et al., 2022	0.14	(-0.22, 0.50)	27.78
Jimeno-Almazan et al., 2022	0.30	(-0.33, 0.93)	18.07
Bagherzadeh et al., 2022_pilates	0.85	(-0.05, 1.74)	11.93
Bagherzadeh et al., 2022_aqua	1.60	(0.59, 2.62)	9.94
Overall (*P* = 0.015; I² = 47%)	0.37	(0.00, 0.75)	100
Pretest-posttest			
Loboda et al., 2022	0.02	(-0.06, 0.10)	39.65
Albu et al., 2021	0.06	(-0.25, 0.37)	18.19
Stavrou et al., 2021	0.23	(-0.21, 0.68)	11.28
Everaerts et al., 2021	0.25	(-0.25, 0.75)	9.48
Nopp et al., 2022	0.40	(0.13, 0.66)	21.40
Overall (*P* = 0.081; *I*² = 58%)	0.15	(-0.02, 0.33)	100

B

FEV1/FVC

Study	Mean Difference	(95%CI)	Weight (%)
RCT or CCT			
Amaral et al., 2022	-0.80	(-4.96, 3.36)	15.19
Jimeno-Almazan et al., 2022	0.80	(-2.33, 3.93)	19.10
Li et al., 2022	3.00	(-0.61, 6.61)	17.16
Campos et al., 2022	4.60	(1.04, 8.16)	17.37
Bagherzadeh et al., 2022_pilates	6.20	(2.08, 10.32)	15.31
Bagherzadeh et al., 2022_aqua	7.00	(3.04, 10.96)	15.87
Overall (*P* < 0.001; *I*² = 58%)	3.41	(1.05, 5.76)	100
Pretest-posttest			
Loboda et al., 2022	-0.95	(-1.81, -0.09)	50.44
Nopp et al., 2022	0.90	(-1.63, 3.43)	27.84
Albu et al., 2021	2.10	(-1.05, 5.25)	21.72
Overall (*P* = 0.812; *I*² = 58%)	0.23	(-1.64, 2.10)	100

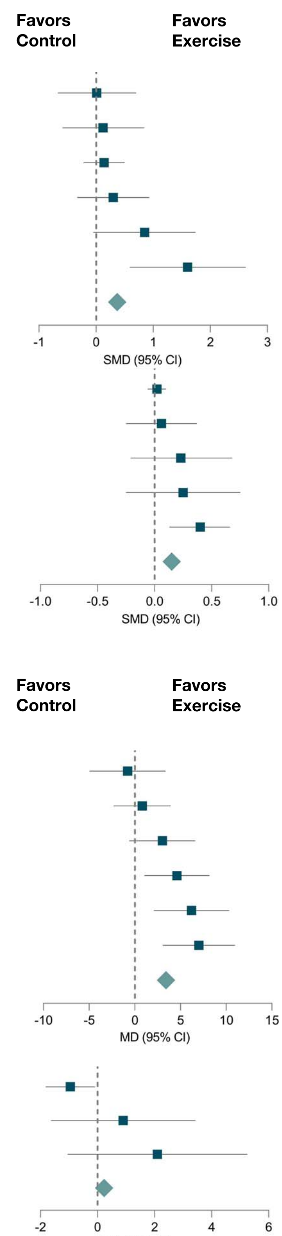

FIGURE 2—Pooled analysis of the effect of physical exercise–based rehabilitation on FEV1 (A) and FEV1/FVC (B). Pilates, Pilates group; Aqua, aqua-Pilates group.

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6-MWT (m)

Study	Mean Difference	(95%CI)	Weight (%)
RCT or CCT			
King et al., 2022	50.50	(-9.38, 110.38)	23.76
Amaral et al., 2022	53.00	(-13.01, 119.01)	23.10
Li et al., 2022	71.30	(43.52, 99.08)	26.54
Dun et al., 2021	194.00	(167.16, 220.84)	26.60
Overall (P = 0.02; I^2 = 94%)	94.76	(14.83, 174.70)	100
Pretest-posttest			
Loboda et al., 2022	31.50	(26.30, 36.70)	23.33
Nopp et al., 2022	62.90	(36.19, 89.61)	21.57
Stavrou et al., 2021	85.40	(42.02, 128.78)	19.13
Mayer et al., 2021	110.00	(58.14, 161.86)	17.74
Everaerts et al., 2021	168.40	(119.56, 217.24)	18.24
Overall (P < 0.001; I^2 = 91%)	87.47	(43.08, 131.87)	100

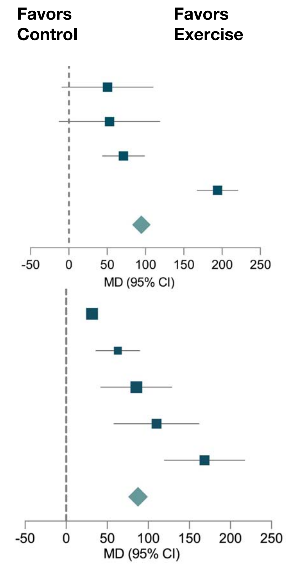


FIGURE 3—Pooled analysis of the effect of physical exercise–based rehabilitation on 6-MWT.

(Supplemental Fig. 1b–c, Supplemental Digital Content, http://links.lww.com/MSS/C932).

A significant increase in the 6-MWT was observed after physical exercise–based rehabilitation compared with the control group (MD = 94.76, 95% CI = 14.83–174.70, I^2 = 94%) and at the pretest (MD = 87.47, 95% CI = 43.08–131.87, I^2 = 91%) (Fig. 3). By contrast, handgrip strength (SMD = 1.46, 95% CI = 0.77–2.14, I^2 = 94%) and STST (SMD = 0.85, 95% CI = 0.68–1.03, I^2 = 0%) were only improved after physical exercise–based rehabilitation in the pretest–posttest design studies (Fig. 4A and B).

By contrast, a significantly improved QoL was observed after physical exercise–based rehabilitation in both the RCT/CCT (SMD = 0.65, 95% CI = 0.33, 0.96, I^2 = 39%) and the pretest–posttest design studies (SMD = 1.82, 95% CI = 1.10–1.97, I^2 = 94%) (Fig. 5). Physical exercise–based rehabilitation significantly decreased the levels of dyspnea (SMD = 0.62, 95% CI = 0.39–0.86, I^2 = 0%), fatigue (SMD = 0.57, 95% CI = 0.15–0.98, I^2 = 0%), and depression (SMD = 0.70, 95% CI = 0.32–1.08, I^2 = 0%) in individuals who had had COVID-19 (Fig. 6A, B and Fig. 7B) than in the control group. However, no improvement in anxiety was found in either the RCT/CCT (SMD = 0.37, 95% CI = −0.06 to 1.36, I^2 = 70%) or the pretest–posttest design studies (SMD = 0.25, 95% CI = −0.13 to 0.63, I^2 = 71%) (Fig. 7A) after physical exercise–based rehabilitation. In addition, cognitive function was only improved after physical exercise–based rehabilitation in the pretest–posttest design studies (SMD = 0.40, 95% CI = 0.23–0.56, I^2 = 0%) (Supplemental Fig. 2, Supplemental Digital Content, Pooled analysis on the effect of physical exercise–based rehabilitation on cognitive function, http://links.lww.com/MSS/C932).

DISCUSSION

The number of individuals with long COVID is notably increasing since the COVID-19 global pandemic, leading to an expanding disease burden of long COVID worldwide. Although many guidelines for self-management and multidisciplinary rehabilitation of long COVID have been implemented (26,60), their effectiveness remains understudied. Physical exercise–based rehabilitation is one of the most promising rehabilitation strategies against long COVID, although its inappropriate implementation could be detrimental to people with post-COVID-19 conditions (22). Thus, whether physical exercise–based rehabilitation is safe and effective for alleviating long COVID remains inconclusive. In the current study, we systematically synthesized published studies that focused on physical exercise–based rehabilitation for long COVID and examined its preventive and therapeutic effects and relative safety in routine clinical practice by performing a meta-analysis. The findings of this review indicate that physical exercise–based rehabilitation is an effective and safe strategy for alleviating long COVID-related symptoms, as characterized by alleviated dyspnea, fatigue, and depression, as well as improved 6-MWT, FEV1/FVC, and QoL. The 6-MWT is routinely applied to assess cardiopulmonary and locomotor functions in clinical practice, including in patients with COVID-19, those who have recovered from COVID-19, and people with post-COVID conditions (60). However, physical exercise–based rehabilitation showed nonsignificant effects on handgrip strength, STST, and anxiety. Moreover, physical exercise–based rehabilitation resulted in limited adverse effects during routine clinical practice for some individuals who had had COVID-19. A major adverse event (i.e., increased dyspnea and exhaustion after training) was only reported during the first week of in-person training by a person who had been admitted to the intensive care unit during COVID-19 (59), whereas minor adverse events were observed in a small number of studies (51,59,61). Overall, physical exercise–based rehabilitation is generally considered safe and effective for individuals with long COVID; however, the

A

Handgrip

Study	Standardized Mean Difference	(95%CI)	Weight (%)
RCT or CCT			
King et al., 2022	0.10	(-0.76, 0.95)	16.96
Jimeno-Almazan et al., 2022	0.15	(-0.48, 0.78)	31.49
Amaral et al., 2022	0.52	(-0.21, 1.25)	23.56
Campos et al., 2022	0.53	(-0.14, 1.19)	27.98
Overall (P = 0.063; I^2 = 0%)	0.33	(-0.02, 0.69)	100
Pretest-posttest			
Stavrou et al. 2021	0.13	(-0.31, 0.57)	13.54
Mayer et al., 2021_right	0.43	(0.03, 0.84)	13.66
Barbara et al. 2022	0.46	(0.17, 0.75)	13.97
Albu et al., 2021	0.47	(0.14, 0.80)	13.88
Mayer et al., 2021_left	0.48	(0.08, 0.89)	13.65
Everaerts et al. 2021	2.58	(1.71, 3.45)	11.65
Nambi et al. 2022_hight	2.63	(1.95, 3.32)	12.56
Nambi et al. 2022_light	7.81	(5.98, 9.65)	7.08
Overall (P < 0.001; I^2 = 94%)	1.46	(0.77, 2.14)	100

B

STST

Study	Standardized Mean Difference	(95%CI)	Weight (%)
RCT or CCT			
Capin et al., 2022	-0.32	(-1.00, 0.36)	26.35
Amaral et al., 2022	0.43	(-0.29, 1.15)	25.45
King et al., 2022	1.03	(0.12, 1.95)	21.72
Jimeno-Almazan et al., 2022	1.10	(0.43, 1.77)	26.48
Overall (P = 0.066; I^2 =70%)	0.54	(-0.13, 1.22)	100
Pretest-posttest			
Mayer et al., 2021	0.68	(0.27, 1.09)	17.91
Nopp et al. 2022	0.74	(0.42, 1.06)	29.62
Stavrou et al. 2021	0.91	(0.39, 1.43)	11.17
Dalbosco-Salas et al. 2021	0.91	(0.60, 1.22)	31.73
Kortianou et al., 2022	1.27	(0.71, 1.84)	9.57
Overall (P < 0.001; I^2 = 0%)	0.85	(0.68, 1.03)	100

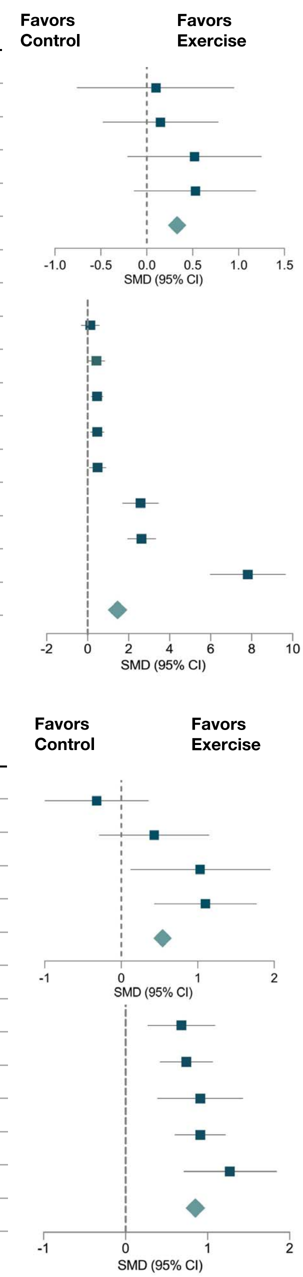


FIGURE 4—Pooled analysis of the effect of physical exercise–based rehabilitation on handgrip strength (A) and STST (B). Left, left hand; Right, right hand.

severity of illness experienced by the patient during the infection should be seriously considered before the implementation of physical exercise–based rehabilitation. More importantly, most physical exercise–based rehabilitation programs were carried out in a clinical setting leading to a low occurrence rate of adverse events (1.2%) (46). Therefore, to avoid inappropriate physical exercise–induced adverse events during the rehabilitation, face-to-face supervision and training at a clinic should be required for physical exercise–based rehabilitation for individuals who have recovered from COVID-19 or are living with long COVID.

The WHO encourages countries to provide people who have had COVID-19 with more health care services following the "three R" principle (recognition, research, and rehabilitation) (62). Previous studies have highlighted the rehabilitation needs of individuals with long COVID even many months after recovery from COVID-19 (63). However, our systematic search identified relatively limited evidence regarding the implementation of physical exercise–based rehabilitation for long COVID, considering the expanding research on COVID-19 worldwide. Despite being one of the most promising strategies for long COVID, the effect of physical exercise–based rehabilitation on long COVID has not been clearly addressed (26). Our meta-analysis provided more solid evidence that physical exercise–based rehabilitation is an effective and relatively safe strategy to alleviate the symptoms of long COVID. However, most of the studies included in this systematic review focused

Quality of life

Study	Standardized Mean Difference	(95%CI)	Weight (%)
RCT or CCT			
King et al., 2022	0.06	(-0.79, 0.92)	9.99
Li et al., 2022	0.46	(0.09, 0.82)	25.38
Romanet et al., 2022	0.53	(0.02, 1.05)	18.85
Jimeno-Almazan et al., 2022	0.60	(-0.04, 1.25)	14.78
Bhandari et al., 2022	0.62	(-0.02, 1.25)	14.98
Bagherzadeh et al., 2022_pilates	1.16	(0.24, 2.08)	8.95
Bagherzadeh et al., 2022_aqua	1.97	(0.90, 3.04)	7.06
Overall ($P < 0.001$; $I^2 = 39\%$)	0.65	(0.33, 0.96)	100
Pretest-posttest			
Daynes et al. 2021	0.41	(0.03, 0.78)	14.49
Mayer et al., 2021	0.70	(0.29, 1.10)	14.39
Dalbosco-Salas et al. 2021	0.87	(0.56, 1.17)	14.68
Nopp et al. 2022	0.92	(0.52, 1.32)	14.40
Albu et al., 2021	1.04	(0.66, 1.43)	14.45
Kortianou et al., 2022	1.63	(0.99, 2.27)	13.49
Nambi et al. 2022_hight	4.91	(3.75, 6.07)	10.84
Nambi et al. 2022_light	15.30	(11.75, 18.85)	3.26
Overall ($P < 0.001$; $I^2 = 94\%$)	1.82	(1.10, 2.54)	100

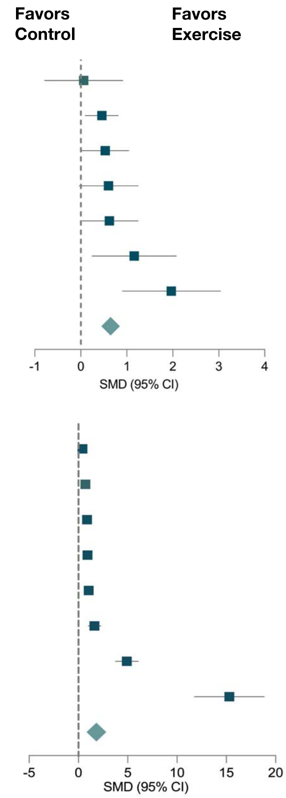


FIGURE 5—Pooled analysis of the effect of physical exercise–based rehabilitation on QoL. Pilates, Pilates group; Aqua, aqua-Pilates group; Hight, high intensity; Light, light intensity.

on hospitalized patients with relatively severe COVID-19, yet those with mild COVID-19 symptoms can also experience long COVID (14). Besides, a novel study has demonstrated the great potential of physical exercise–based rehabilitation in alleviating long COVID-related symptoms in nonhospitalized individuals (64). Therefore, further large-scale studies on physical exercise as a rehabilitation strategy against long COVID in nonhospitalized patients with COVID-19, patients with mild symptoms during the initial infection, or patients with COVID-19 caused by various SARS-CoV-2 variants from different counties are needed.

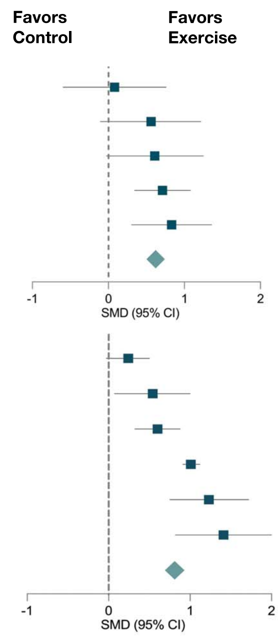
COVID-19 was originally considered to be a pulmonary disease; however, studies have revealed that SARS-CoV-2 affects a wide range of tissues and organs throughout the human body, such as the heart, lungs, brain, digestive tract, muscle, and kidneys (12). This results in the complex clinical manifestations of COVID-19 and long COVID. Many common symptoms of long COVID were reported in the studies included herein, including dyspnea, fatigue, chest pain, neurological or cognitive impairment, and persistent cough (24). Physical exercise–based rehabilitation showed significant effects on dyspnea and fatigue based on the data from included studies; however, more studies are warranted to examine its therapeutic effects on the other common symptoms. Besides, the physical exercise–based rehabilitation in the included studies was commonly a mixed-type physical exercise–based rehabilitation program, largely comprising aerobic, resistance, and stretching exercises. Because long COVID has widespread symptoms, a mixed-type physical exercise program may provide a more comprehensive health benefit than a single type of exercise-based rehabilitation, such as breathing exercises. Although yoga was used in one of the studies (40), the great potential of mind–body exercises, such as Qigong, yoga, mindfulness, and Tai Chi, has not yet been fully exploited as they may be more suitable for frail patients with long COVID (65). However, a combination of mind–body exercises with other mixed-type physical exercise programs should be taken into consideration when developing a more effective rehabilitation program for those living with long COVID.

Furthermore, customized exercise prescriptions for individuals with unique symptoms of long COVID are also required as inappropriate physical exercise can worsen long COVID symptoms, such as postexertional symptom exacerbation (66). Therefore, evidence-based, comprehensive, and precise guidelines for physical exercise–based rehabilitation for distinctive symptoms of long COVID remain warranted. More importantly, our meta-analysis of RCT or CCT revealed the benefit of physical exercise–based rehabilitation in improving long COVID-related pulmonary dysfunction and locomotor impairment. Previous studies have documented that inpatient physical exercise–based rehabilitation provided to patients from admission to discharge effectively improves locomotor, pulmonary, and physical functions, particularly in severe cases (67–69). Nevertheless, the long-term effect of inpatient

A

Dyspnea

Study	Standardized Mean Difference	(95%CI)	Weight (%)
RCT or CCT			
Capin et al., 2022	0.08	(-0.60, 0.76)	12.35
Campos et al., 2022	0.56	(-0.11, 1.22)	12.65
Jimeno-Almazan et al., 2022	0.61	(-0.03, 1.25)	13.70
Li et al., 2022	0.71	(0.34, 1.08)	41.16
Romanet et al., 2022	0.83	(0.30, 1.36)	20.14
Overall (P < 0.001; I^2 = 0%)	0.62	(0.39, 0.86)	100
Pretest-posttest			
Nopp et al. 2022	0.24	(-0.03, 0.50)	18.56
Stavrou et al. 2021	0.54	(0.07, 1.00)	15.00
Dalbosco-Salas et al. 2021	0.60	(0.32, 0.88)	18.31
Loboda et al., 2022	1.01	(0.91, 1.12)	20.53
Mayer et al., 2021	1.23	(0.75, 1.72)	14.74
Kortianou et al., 2022	1.41	(0.82, 2.00)	12.86
Overall (P < 0.001; I^2 = 87%)	0.81	(0.46, 1.15)	100



B

Fatigue

Study	Standardized Mean Difference	(95%CI)	Weight (%)
RCT or CCT			
King et al., 2022	0.13	(-0.80, 1.05)	20.34
Campos et al., 2022	0.50	(-0.17, 1.17)	39.22
Jimeno-Almazan et al., 2022	0.85	(0.20, 1.51)	40.44
Overall (P = 0.008; I^2 = 0%)	0.57	(0.15, 0.98)	100
Pretest-posttest			
Kortianou et al., 2022	0.13	(-0.29, 0.55)	11.74
Stavrou et al. 2021	0.35	(-0.10, 0.80)	10.90
Daynes et al. 2021	0.37	(-0.00, 0.74)	13.21
Loboda et al., 2022	0.45	(0.36, 0.54)	22.33
Dalbosco-Salas et al. 2021	0.54	(0.27, 0.82)	16.26
Nopp et al. 2022	0.76	(0.41, 1.12)	13.61
Albu et al., 2021	1.24	(0.83, 1.66)	11.94
Overall (P < 0.001; I^2 = 69%)	0.54	(0.34, 0.75)	100

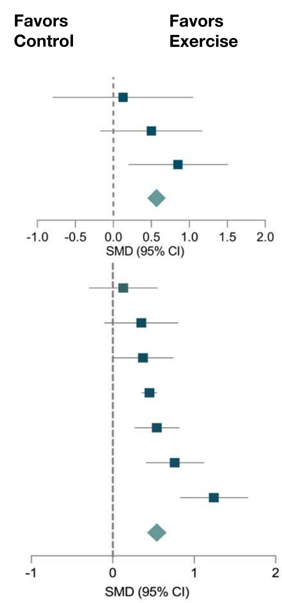


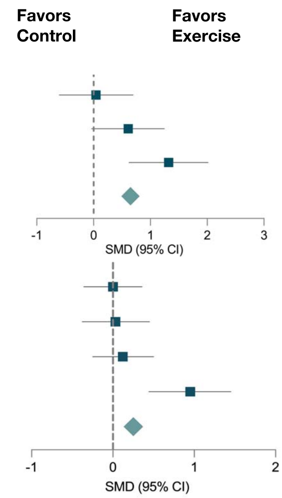
FIGURE 6—Pooled analysis of the effect of physical exercise–based rehabilitation on dyspnea (A) and fatigue (B).

rehabilitation on long COVID remains unclear, as the follow-up measurements in these studies were usually lacking, and no effect of rehabilitation on long COVID has been reported (70). To the best of our knowledge, our study is the first systematic review and meta-analysis to provide solid evidence that physical exercise–based rehabilitation is an effective strategy against specific symptoms of long COVID, which was determined using the 6-MWT, FEV1/FVC, and validated scales. The meta-analysis of RCT/CCT and one-group pretest–posttest studies in our review also indicated that physical exercise–based rehabilitation can serve as a routine clinical practice for patients who have recovered from COVID-19 to alleviate long COVID, as characterized by improved MIP, TLCO, 6-MWT, handgrip strength, and STST. These improvements are probably attributed to the beneficial effects of physical exercise–related rehabilitation on the progression of long COVID or the fitness of participants. Although the one-group pretest–posttest design failed to demonstrate the therapeutic effect of physical exercise–based rehabilitation on long COVID owing to the lack of control groups, these results suggest that physical exercise–based rehabilitation can serve as a standard treatment in the control groups in future RCT designed to investigate other rehabilitation strategies for long COVID, such as continuous positive airway pressure, olfactory rehabilitation, and neurorehabilitation (71–73). It should be noted that the implementation of physical exercise–based rehabilitation may be introduced much longer than 3 months postinfection, which may lead to an underestimation of the effects of physical exercise–based rehabilitation if

A

Anxiety

Study	Standardized Mean Difference	(95%CI)	Weight (%)
RCT or CCT			
Campos et al., 2022	0.04	(-0.61, 0.70)	33.64
Jimeno-Almazan et al., 2022	0.61	(-0.04, 1.25)	34.06
Bhandari et al., 2022	1.32	(0.62, 2.02)	32.30
Overall (*P* = 0.073; I^2 = 70 %)	0.65	(-0.06, 1.36)	100
Pretest-posttest			
Daynes et al. 2021	0.00	(-0.36, 0.36)	26.93
Everaerts et al. 2021	0.03	(-0.38, 0.45)	24.78
Mayer et al., 2021	0.12	(-0.25, 0.50)	26.43
Kortianou et al., 2022	0.95	(0.44, 1.45)	21.85
Overall (*P* = 0.200; I^2 = 71%)	0.25	(-0.13, 0.63)	100



B

Depression

Study	Standardized Mean Difference	(95%CI)	Weight (%)
RCT or CCT			
Campos et al., 2022	0.36	(-0.31, 1.02)	33.37
Jimeno-Almazan et al., 2022	0.76	(0.11, 1.41)	34.54
Bhandari et al., 2022	1.00	(0.32, 1.67)	32.09
Overall (*P* < 0.001; I^2 = 0%)	0.70	(0.32, 1.08)	100
Pretest-posttest			
Daynes et al. 2021	0.25	(-0.11, 0.61)	29.26
Everaerts et al. 2021	0.29	(-0.21, 0.79)	21.55
Mayer et al., 2021	0.33	(-0.05, 0.71)	28.18
Kortianou et al., 2022	1.00	(0.49, 1.51)	21.02
Overall (*P* = 0.006; I^2 = 52%)	0.44	(0.13, 0.75)	100

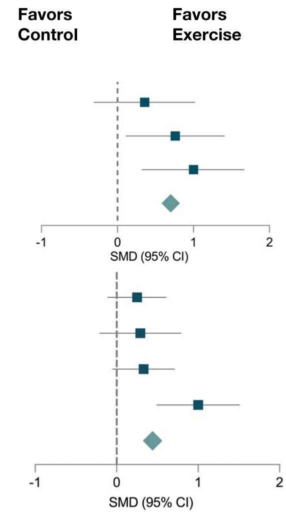


FIGURE 7—Pooled analysis of the effect of physical exercise–based rehabilitation on anxiety (A) and depression (B).

participants spontaneously recovered from long COVID or received any treatment or rehabilitation before the baseline assessment. Besides, ethical issues should be considered in the controls experiencing long COVID but receiving no treatments in RCT or CCT.

In addition, the potential adverse effects of physical exercise on those with long COVID may be attributed to the unsupervised intensity and timing of exercise and poor general health of individuals who had had COVID-19. Resuming physical exercise shortly after infection and intense exercise can be detrimental to people who have recovered from COVID-19 (22,23). High-intensity physical exercise seems to deliver fewer benefits than light-intensity physical exercise in the rehabilitation of patients with long COVID, as reported by a previous study, although further evidence is needed (39). In our systematic review, very limited adverse events were reported during physical exercise–based rehabilitation, which can be largely attributed to the supervision of rehabilitation and the relatively good health status of participants. The overall beneficial effects of physical exercise–based rehabilitation for long COVID based on the meta-analysis can be attributed to the appropriate intensity, timing, and supervision of physical exercise applied in most studies included in this systematic review. Therefore, a proper level and supervised physical exercise–based rehabilitation is generally beneficial for individuals with long COVID.

This study has some limitations. Although physical exercise served as the main rehabilitation strategy for long COVID in the included studies, other types of rehabilitation were also included in some of the studies, such as educational and psychological strategies. Thus, it was difficult to distinguish the sole effects of physical exercise on long COVID. Moreover, long COVID-related outcomes were measured at least 3 months postinfection, and information on the duration of the symptoms was usually missing. Future studies on the effects of physical exercise–based rehabilitation on long COVID should collect more complete information regarding the duration of symptoms and the presence of any other alternative diagnosis regarding long COVID. Another key limitation was the relatively small number of studies on physical exercise–based rehabilitation to attenuate long COVID, which led to limited populations, types of physical exercise, and types of long COVID-related symptoms. Nevertheless, the findings of this systematic review and meta-analysis provide evidence that physical exercise–based rehabilitation is a beneficial routine clinical practice for individuals who had COVID-19 to alleviate long COVID.

CONCLUSIONS

This systematic review and meta-analysis provided evidence that physical exercise–based rehabilitation is an efficient and safe rehabilitation strategy for, at least, several specific symptoms of long COVID. As physical exercise is known for its cost-efficiency and accessibility, the implementation of physical exercise–based rehabilitation in people who have recovered from COVID-19 is a promising strategy to reduce the global burden of long COVID on individuals and society. Nevertheless, large-scale studies on physical exercise–based rehabilitation for alleviating various types of long COVID and optimal exercise prescriptions remain warranted.

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The authors declare that they have no competing interests. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

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