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Physical exercise-related manifestations of long COVID: A systematic review and meta-analysis

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A R T I C L E I N F O

Keywords:
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PASC
Exercise capacity
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VO_2max

A B S T R A C T

Objective: This study aims to systematically assess physical exercise-related symptoms of post-acute sequelae of SARS-CoV-2 infection (PASC or long COVID) in coronavirus disease 2019 (COVID-19) survivors.
Methods: Eight databases were systematically searched on March 03, 2024. Original studies that compared physical exercise-related parameters measured by exercise testing between COVID-19 survivors who recovered from SARS-CoV-2 infection over 3 months and non-COVID-19 controls were included. A random-effects model was utilized to determine the mean differences (MDs) or standardized MDs in the meta-analysis.
Results: A total of 40 studies with 6241 COVID-19 survivors were included. The 6-min walk test, maximal oxygen consumption (VO_2max), and anaerobic threshold were impaired in COVID-19 survivors 3 months post-infection compared with non-COVID-19 controls in exercise testing, while VO_2 were comparable between the two groups at rest. In contrast, no differences were observed in SpO_2, heart rate, blood pressure, fatigue, and dyspnea between COVID-19 survivors and non-COVID-19 controls in exercise testing.
Conclusion: The findings suggest an underestimation of the manifestations of PASC. COVID-19 survivors also harbor physical exercise-related symptoms of PASC that can be determined by the exercise testing and are distinct from those observed at rest. Exercise testing should be included while evaluating the symptoms of PASC in COVID-19 survivors.

1. Introduction

With the ongoing global coronavirus disease 2019 (COVID-19) pandemic and the increase in the number of COVID-19 survivors, mounting evidence has documented that some COVID-19 survivors experience persistent post-acute sequelae of SARS-CoV-2 infection (PASC or long COVID), which is defined as the new symptoms 3 months after infection with no other explanation.[1] The global prevalence of PASC was estimated at approximately 30 % and 50 % at 90 and 120 days post-SARS-CoV-2 infection, respectively, which was affected by age, sex, ethnicity, pre-infection health status, and COVID-19 severity.[2] In addition, the manifestations of PASC are highly complex and widespread, mainly including fatigue, "brain fog", anxiety, depression, insomnia, dyspnea, and chest pain; and a wide array of rare manifestations have also been reported.[3] As the disease burden of PASC is a huge challenge to the healthcare system worldwide, prompt and accurate diagnosis of PASC is required. However, most previous studies used self-reported symptoms by COVID-19 survivors because of the limited objective assessment tools.[1,3] Therefore, the prevalence, duration, and severity of PASC are most likely underestimated.

Objectively-measured physical activity (PA) was reduced in COVID-19 survivors, which can last for months after SARS-CoV-2 infection.[4] However, there are several barriers for COVID-19 survivors return to normal exercise training.[5] For example, some manifestations in PASC that are related to physical exercise have long been featured in PASC, such as muscle or joint pain, post-exertional malaise, and post-exertional fatigue.[6] More importantly, PA shortly after recovery from COVID-19 was found to be one of the major triggers of PASC, because some PASC related symptoms worsening following physical or mental exercise, typically 12–48 h after, which is also known as post-exertional

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malaise or post-exertional symptom exacerbation.[7,8] This suggests that the physical exercise-related and possibly other manifestations of PASC are affected by daily activities. However, most of these symptoms were subjectively reported by COVID-19 survivors without appropriate controls, while few utilized exercise testings.[9,10] In this case, we may underestimate physical exercise-related manifestations of PASC in COVID-19 survivors, especially after exercise, which may increase the risk of future mortality and disease. Thus, a comprehensive picture of physical exercise-related manifestations of PASC is warranted.

There are several systematic reviews that have summarized the symptoms of PASC, including fatigue, headache, attention disorder, hair loss, and dyspnea.[2,11,12] However, none of the above studies focused on exercise-related manifestations, especially the manifestations after exercise tests. Therefore, we conducted a systematic review to synthesize the available evidence on the physical exercise-related PASC measured using exercise testing in COVID-19 survivors and non-COVID-19 controls at least 3 months post-infection. All the physiological and clinical parameters measured in the exercise testing were analyzed to characterize the physical exercise-related manifestations of PASC. A meta-analysis was performed between COVID-19 survivors and non-COVID-19 controls at rest/pre-exercise and post-exercise to determine the differences in manifestations of PASC between the at rest and in exercise testing conditions.

2. Materials and methods

This systematic review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022331179) and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[13]

2.1. Search strategy

Databases were searched from inception through March 03, 2024, including Medline, Embase, Global Health (Ovid), CINAHL (EBSCO), and Web of Science. We also manually searched the reference lists of included studies and Word Health Organization (WHO) Global Research Database on COVID-19, LitCovid, and Google Scholar (the first 500 titles). Identified articles were imported into the EndNote reference (Clarivate), and duplicates were removed before the screening. Full search items used were presented in eTable 1 in the Supplement.

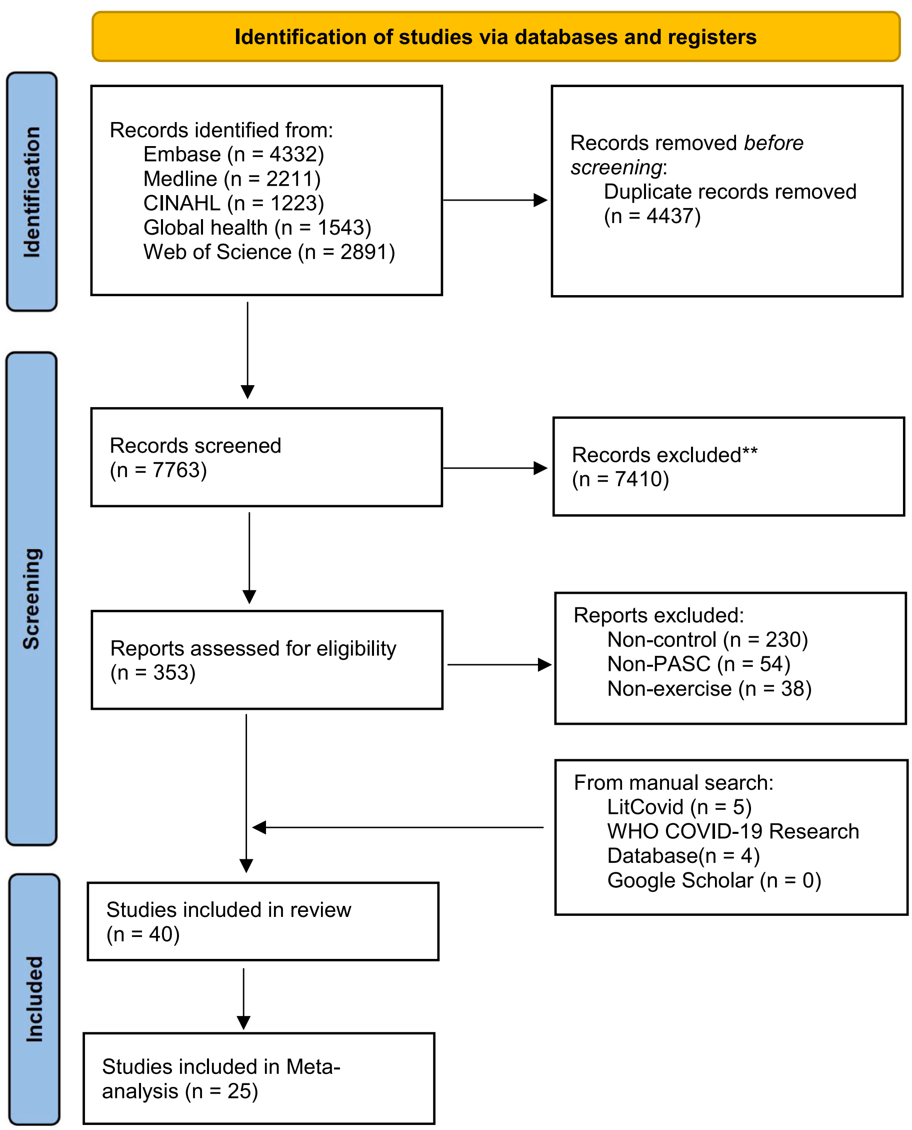
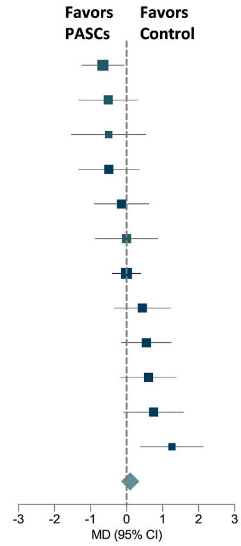


Fig. 1. Flow diagram of study identification and Selection
Abbreviations: Pasc, post-acute sequelae of SARS-CoV-2 infection; WHO, World Health Organization.

A VO_2 at rest

Source	COVID-19 survivor, No.	Control, No.	MD (95%CI)	Weight %
Longobardi et al,[31] 2022	35	18	-0.66 (-1.24 to -0.07)	10.3
Ladlow et al,[30] 2022c	34	7	-0.51 (-1.33 to 0.31)	7.7
Ladlow et al,[30] 2022b	8	7	-0.50 (-1.53 to 0.54)	6.0
Ladlow et al,[30] 2022a	27	7	-0.49 (-1.33 to 0.35)	7.6
Brown et al,[24] 2022a	20	10	-0.14 (-0.90 to 0.62)	8.3
Ladlow et al,[30] 2022d	18	7	0.00 (-0.87 to 0.87)	7.3
Szekely et al,[36] 2021	71	36	0.00 (-0.40 to 0.40)	12.5
Beaudry et al,[23] 2022b	14	12	0.44 (-0.34 to 1.22)	8.1
Beaudry et al,[23] 2022a	28	12	0.55 (-0.14 to 1.24)	9.1
Brown et al,[24] 2022b	20	10	0.61 (-0.17 to 1.38)	8.2
Joris et al,[29] 2022b	23	8	0.75 (-0.08 to 1.58)	7.7
Joris et al,[29] 2022a	31	7	1.26 (0.39 to 2.13)	7.3
Random effect model (P = 0.55; I^2 = 57%)			0.10 (-0.22 to 0.42)	



B VO_2max

Source	COVID-19 survivor, No.	Control, No.	MD (95%CI)	Weight %
Singh et al,[33] 2022	21	25	-16.80 (-25.21 to -8.39)	3.4
Pleguezuelos et al,[32] 2021	9	7	-15.01 (-18.51 to -11.51)	5.5
Ladlow et al,[30] 2022a	71	36	-14.00 (-23.89 to -4.11)	2.9
Dotan et al,[26] 2022b	31	15	-12.00 (-19.62 to -4.38)	3.7
Ladlow et al,[30] 2022b	20	10	-11.30 (-22.03 to -0.57)	2.7
Ladlow et al,[30] 2022c	8	7	-9.50 (-19.50 to 0.50)	2.9
Vonbank et al,[37] 2021b	13	7	-8.30 (-12.32 to -4.28)	5.3
Beaudry et al,[23] 2022a	35	18	-8.00 (-14.09 to -1.91)	4.4
Frizzelli et al,[42] 2022	42	40	-8.00 (-11.93 to -4.07)	5.3
Cassar et al,[10] 2021	28	12	-7.60 (-11.84 to -3.36)	5.2
Beaudry et al,[23] 2022a	27	7	-5.00 (-12.31 to 2.31)	3.9
Jamieson et al,[43] 2024	26	19	-5.00 (-7.28 to -2.72)	5.9
Longobardi et al,[31] 2022	16	16	-4.55 (-7.14 to -1.96)	5.8
Contreras et al,[41] 2023	77	766	-3.90 (-5.42 to -2.38)	6.1
Ramîrez-Vélez et al,[45] 2023	71	63	-3.50 (-5.48 to -1.52)	6.0
Dotan et al,[26] 2022a	34	7	-2.00 (-11.16 to 7.16)	3.2
Vonbank et al,[37] 2021a	79	25	-1.40 (-4.95 to 2.15)	5.5
Alba et al,[9] 2021	14	12	-0.50 (-5.05 to 4.05)	5.1
Ladlow et al,[30] 2022d	20	10	0.40 (-9.89 to 10.69)	2.8
Stavrou et al,[35] 2021	18	7	1.70 (0.73 to 2.67)	6.2
Joris et al,[29] 2021a	40	40	2.00 (-4.19 to 8.19)	4.3
Joris et al,[29] 2021b	18	18	11.10 (3.15 to 19.05)	3.6
Random effect model (P < 0.00001; I^2 = 89%)			-5.22 (-7.53 to -2.91)	

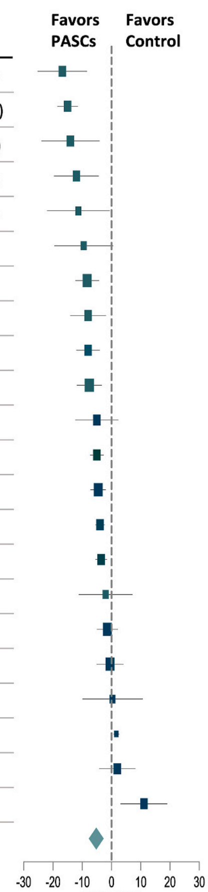


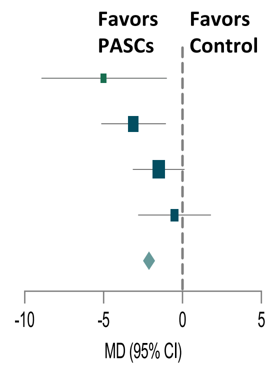
Fig. 2. Forest Plot of VO_2max and VO_2 at Rest between COVID-19 Survivors and Non-COVID-19 Controls.
Abbreviations: COVID-19, coronavirus disease 2019; PASC, Post-Acute Sequelae of SARS-CoV-2 Infection; VO_2, oxygen consumption; VO_2max, maximal oxygen consumption.

2.2. Eligibility criteria

Two reviewers (X.C., C.Z.) independently screen the titles, abstract, and full texts to identify the eligible articles. Any disagreements were resolved by discussion or a third reviewer (J.C.). The inclusion criteria are original articles written in English and included physical exercise or physical activity testing in both COVID-19 survivors and non-COVID-19 controls. To determine the physical exercise-related manifestations of PASC in COVID-19 survivors, physical exercise or PA-related measurements were conducted at least 3 months post-SARS-CoV-2 infection.[14]

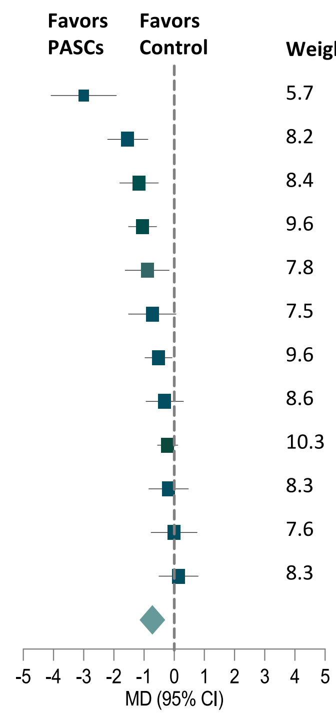
A **Anaerobic threshold**

Source	COVID-19 survivor, No.	Control, No.	MD (95%CI)	Weight %
Frizzelli et al,[42] 2022	42	40	-5.00 (-8.93 to -1.07)	11.8
Szekely et al,[36] 2021	71	36	-3.10 (-5.14 to -1.06)	28.4
Cassar et al,[10] 2021	31	23	-1.50 (-3.13 to 0.13)	34.9
Alba et al,[9] 2021	18	18	-0.50 (-2.80 to 1.80)	24.9
Random effect model (P = 0.006; I^2 = 44%)			-2.12 (-3.64 to -0.60)	



B **Peak workload**

Source	COVID-19 survivor, No.	Control, No.	SMD (95%CI)	Weight %
Pleguezuelos et al,[32] 2021	15	15	-3.00(-4.08 to -1.91)	5.7
Vonbank et al,[37] 2021b	21	25	-1.54 (-2.20 to -0.87)	8.2
Jamieson et al,[43] 2024	26	19	-1.16 (-1.80 to -0.52)	8.4
Frizzelli et al,[42] 2022	42	40	-1.05 (-1.51 to -0.58)	9.6
Janssen et al,[28] 2022	16	16	-0.89 (-1.62 to -0.16)	7.8
Brown et al,[24] 2022a	20	10	-0.72 (-1.51 to 0.06)	7.5
Vonbank et al,[37] 2021a	79	25	-0.52 (-0.97 to -0.06)	9.6
Joris et al,[29] 202a	31	15	-0.31 (-0.93 to 0.31)	8.6
Ramîrez-Vélez et al,[45] 2023	71	63	-0.21 (-0.55 to 0.13)	10.3
Alba et al,[9] 2021	18	18	-0.18 (-0.84 to 0.47)	8.3
Brown et al,[24] 2022a	20	10	0.00 (-0.76 to 0.76)	7.6
Joris et al,[29] 202b	23	15	0.15 (-0.50 to 0.80)	8.3
Random effect model (P = 0.0001; I^2 = 77%)			-0.72 (-1.08 to -0.35)	



C **Peak lactate**

Source	COVID-19 survivor, No.	Control, No.	MD (95%CI)	Weight %
Ladlow et al,[30] 2022a	27	7	-2.70 (-4.11 to -1.29)	14.8
Vonbank et al,[37] 2021b	21	25	-2.02 (-3.26 to -0.78)	17.4
Vonbank et al,[37] 2021a	77	25	-1.35 (-2.19 to -0.51)	26.4
Ladlow et al,[30] 2022c	34	7	-1.10 (-2.45 to 0.25)	15.6
Janssen et al,[28] 2022	16	16	-0.40 (-3.25 to 2.45)	4.8
Ladlow et al,[30] 2022b	8	7	-0.20 (-2.26 to 1.86)	8.3
Ladlow et al,[30] 2022d	18	7	-0.01 (-1.67 to 1.47)	12.7
Random effect model (P < 0.001; I^2 = 32%)			-1.33 (-1.98 to -0.67)	

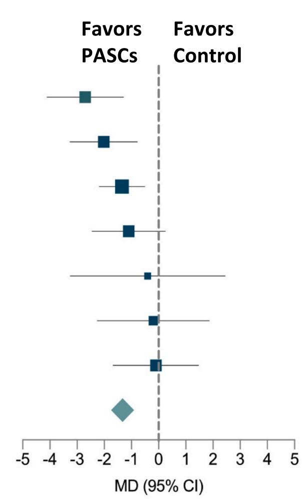


Fig. 3. Forest Plot of Anaerobic Capacity between COVID-19 Survivors and Non-COVID-19 Controls.
Abbreviations: COVID-19, coronavirus disease 2019; PASC, Post-Acute Sequelae of SARS-CoV-2 Infection.

Since many studies only reported time from discharge, studies with measurements at least 2 months post-discharge from the hospital were also included. The exclusion criteria are 1) studies without non-COVID-19 control groups; 2) studies that did not include physical exercise or PA testing; 3) studies that did not evaluate physical exercise-related manifestations; 4) studies that did not focus on long COVID; and 5) studies written in languages other than English.

2.3. Outcomes and data extraction

Primary outcomes included 6-min walk test (6MWT), maximal oxygen consumption (VO_2max), anaerobic threshold (AT), oxygen saturation (SpO_2), heart rate (HR), blood pressure (BP), fatigue, dyspnea, and exercise duration. Secondary outcomes included PA, O_2 pulse, breathing reserve (BR), end-tidal CO_2 ($ETCO_2$), peak ventilation (peak VE), VE per unit carbon dioxide production (VE/VCO_2), respiratory exchange rate (RER), cardiac output, peak lactate, and peak workload. Data was extracted independently by two reviewers (C.Z., J.C.), and discrepancies were resolved by discussion with a third reviewer (X.C.) until consensus was reached. Information and data of study characteristics were extracted using a standard form, including bibliographic information, study design, participants' characteristics, information of SARS-Cov-2 infection, type of exercise, and primary and secondary outcomes.[15] Mean and standard deviation (S.D.) of primary and secondary outcomes will be extracted, and missing data will be obtained from the authors of the studies or extracted by using WebPlotDigitizer if data is available in the graphs.[16]

2.4. Quality assessment

Risk of bias was assessed by two independent reviewers (K.W., Z.D.) using the Newcastle-Ottawa quality assessment scale (NOS) cohort studies, NOS case-controlled studies, and Agency for Healthcare Research and Quality (AHRQ) checklist for cross-sectional studies.[17,18] The discrepancies between the two reviewers were resolved by consensus after consulting a third reviewer (C.Z.).

2.5. Data analysis

Meta-analysis was performed to assess the differences in physical exercise-related outcomes between COVID-19 survivors and non-COVID-19 controls using Review Manager (version 5.4.1; Cochrane Collaboration, Oxford, UK) software if the targeted outcomes were reported in at least three studies. Considering the variance in exercise tests and different in severity of COVID-19 survivors, random effect models was selected which uses both the sampling error and the between-study variance to estimate the overall effect size.[19] The model was utilized to analyze the pooled effects estimated on the basis of the effects, and mean differences (MDs) or standardized mean differences (SMDs) with 95 % confidence intervals (CIs) were used where appropriate. Heterogeneity was evaluated using g Cochran's χ^2 test and Higgins's I^2 test.[20] I^2 value was used to evaluate study heterogeneity, including low (25 %), moderate (50 %), and high (75 %) heterogeneity. A *P*-value less than 0.05 indicates statistically significant. For the meta-analysis with I^2 greater than 50 %, we conducted sensitivity analyses. This involved excluding one study at a time and evaluating the impact of removing each study on the overall results and the between-study heterogeneity. In addition, publication bias was assessed by using the funnel plot, Begg and Mazumdar's rank correlation test, and Egger's regression.[21,22] The trim and fill method was used to estimate the "missing" studies, if any, in the funnel plots, and adjusted values (random effect) were reported using Comprehensive Meta-Analysis Software 2.0 (Biostat Inc., Englewood, NJ).

3. Results

3.1. Study selection

The database search yielded 12,200 records, and 353 full texts were screened after removing duplicates and assessing the titles and abstracts. In addition, a manual search yielded 687, 374, and 500 records from the WHO Global Research Database on COVID-19, LitCovid, and Google Scholar, respectively. We finally identified 40 studies, of which 25 were further included in the meta-analysis[9,10,23–45] and 15 were excluded owing to incomplete information or data.[46–60] The detailed search results are presented in the PRISMA flowchart in Fig. 1.

3.2. Study characteristics

A summary of the study characteristics of the included articles is shown in eTable 2. Overall, a total of 6241 COVID-19 survivors were presented in the included studies; at least 3428 and 378 of them had been hospitalized and admitted to the intensive care unit, respectively. Besides, at least 8211 non-COVID-19 participants served as the controls, whereas three studies did not report the sample size of the control group[49,51,52] and two studies were self-control studies.[38,54] Most of the included studies were cohort, cross-sectional and case-control studies, while one did not report the study design.[34] In addition, included studies were published in 2021–2024 and from several countries, including seven from United Kingdom,[10,24,30,38,40,43,55]four each from the United States[9,33,41,54] and Spain,[32,44,45,59] three each from China,[25,48,51] Netherlands,[28,46,60] two each from Canada,[23,50] Brazil,[31,56] Italy,[27,42] Turkey,[34,58] Austria,[37,57] and Israel,[26,36] and one each from Ecuador,[47] Belgium,[29] Egypt,[49] Norway,[52] Greece,[35] Switzerland,[53] and Sweden.[39] However, no studies from South Asian and African countries were found.

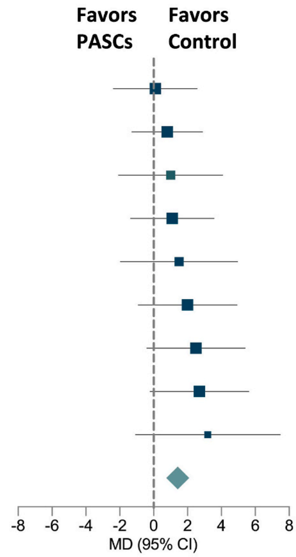
The physical exercise-related manifestations of PASC were assessed in the included studies using cardiopulmonary exercise testing (CPET),[9,10,23,24,26,29–33,36,37,40–43,52] 6MWT,[25,26,34,35,39,44,49,50,57] personalized exercise testing,[28,58] and/or physical exercise/physical activity-related questionnaires[27,30,31,34,38,43,45–48,50,51,53–56,59,60] in the included studies. Primary and secondary outcomes were measured prior to and/or post exercise testing in both COVID-19 survivors and non-COVID-19 controls at least 3 months post-SARS-CoV-2 infection (from 3 to 15 month). Additional information regarding the physical exercise-related outcomes in the included studies is presented in eTable 2.

3.3. Meta-analysis

A visual representation of the distribution of the study effects is shown in forest plots. Outcomes of aerobic exercise capacity, including VO_2max (MD, −5.22; 95 % CI, −7.53 to −2.91, $I^2 = 89$ %, $P < 0.001$) (Fig. 2B) and 6MWT (MD, −67.24; 95 % CI, −114.25 to −20.22, $I^2 = 89$ %, $P = 0.005$) (eFigure1 in the Supplement), were impaired in COVID-19 survivors than non-COVID-19 controls. Importantly, VO_2 was comparable between the two groups at rest (Fig. 2A). In addition, outcomes of anaerobic exercise capacity were also decreased in COVID-19 survivors than in non-COVID-19 controls, such as AT (MD, −2.12; 95 % CI, −3.64 to −0.60, $I^2 = 44$ %, $P = 0.006$), peak workload (SMD, −0.72; 95 % CI, −1.08 to −0.35, $I^2 = 77$ %, $P < 0.001$), and peak lactate (MD, −1.33; 95 % CI, −1.98 to −0.67, $I^2 = 32$ %, $P < 0.001$) (Fig. 3). These impairments may, at least partially, account for the physical inactivity in COVID-19 survivors (SMD, −0.73; 95 % CI, −1.22 to −0.23, $I^2 = 95$ %, $P = 0.004$) (eFig. 2 in the Supplement). In addition, outcomes of respiratory functions, including O_2 pulse (MD, −1.62; 95 % CI, −2.30 to −0.94, $I^2 = 6$ %, $P < 0.001$), RER (MD, −0.02; 95 % CI, −0.04 to −0.01, $I^2 = 23$ %, $P = 0.006$), BR (MD, −4.82; 95 % CI, −9.56 to −0.08, $I^2 = 66$ %, $P = 0.05$), and $ETCO_2$ (MD, −1.10; 95 % CI, −2.15 to −0.04, $I^2 = 0$ %, $P = 0.04$), were also impaired in COVID-19 survivors than in non-COVID-19 controls after exercise testing (eFigs. 3–6 in the Supplement). In contrast, no

A **VE/VCO_2 at rest**

Source	COVID-19 survivor, No.	Control, No.	MD (95%CI)	Weight %
Ladlow et al,[30] 2022d	18	7	0.10 (-2.38 to 2.58)	14.2
Vonbank et al,[37] 2021a	79	25	0.80 (-1.29 to 2.89)	19.9
Beaudry et al,[23] 2022b	14	12	1.00 (-2.08 to 4.08)	9.1
Szekely et al,[36] 2021	71	36	1.10 (-1.37 to 3.57)	14.3
Vonbank et al,[37] 2021b	21	25	1.50 (-1.96 to 4.96)	7.3
Beaudry et al,[23] 2022a	28	12	2.00 (-0.92 to 4.92)	10.2
Ladlow et al,[30] 2022c	34	7	2.50 (-0.41 to 5.41)	10.3
Ladlow et al,[30] 2022a	27	7	2.70 (-0.22 to 5.62)	10.2
Ladlow et al,[30] 2022b	8	7	3.20 (-1.07 to 7.47)	4.8
Random effect model (*P* = 0.003; I^2 = 0%)			1.42 (0.48 to 2.35)	



B **VE/VCO_2 after exercise**

Source	COVID-19 survivor, No.	Control, No.	MD (95%CI)	Weight %
Joris et al,[29] 2022b	23	15	-6.10 (-10.04 to -2.16)	3.7
Contreras et al,[41] 2023	77	766	-1.00 (-2.15 to 0.15)	7.1
Szekely et al,[36] 2021	71	36	-0.90 (-2.10 to 0.30)	7.1
Ladlow et al,[30] 2022d	18	7	-0.80 (-3.63 to 2.03)	5.0
Longobardi et al,[31] 2022	35	18	-0.60 (-3.85 to 2.65)	4.5
Beaudry et al,[23] 2022b	14	12	1.00 (-1.26 to 3.26)	5.7
Chamley et al,[40] 2024a	52	13	1.10 (-1.01 to 3.21)	5.9
Alba et al,[9] 2021	18	18	1.40 (-0.74 to 3.54)	5.9
Joris et al,[29] 2021a	31	15	1.50 (-2.89 to 5.89)	3.3
Ladlow et al,[30] 2022b	8	7	1.80 (-2.61 to 6.21)	3.3
Ladlow et al,[30] 2022c	34	7	1.90 (-0.89 to 4.69)	5.0
Beaudry et al,[23] 2022a	28	12	2.00 (-0.17 to 3.83)	6.3
Dotan et al,[26] 2022a	13	7	2.00 (-4.32 to 8.32)	2.1
Jamieson et al,[43] 2024	26	19	2.30 (0.81 to 3.79)	6.7
Cassar et al,[10] 2021	31	23	3.10 (1.27to 4.93)	6.3
Ladlow et al,[30] 2022a	27	7	3.40 (0.17 to 6.63)	4.5
Chamley et al,[40] 2024b	36	13	3.60 (1.39 to 5.81)	5.8
Frizzelli et al,[42] 2022	42	40	4.00 (2.27 to 5.73)	6.4
Dotan et al,[26] 2022b	9	7	5.00 (-1.41 to 11.41)	2.0
Singh et al,[33] 2022	10	10	8.00 (3.62 to 12.38)	3.3
Random effect model (*P* = 0.006; I^2 = 75%)			1.48 (0.43 to 2.54)	

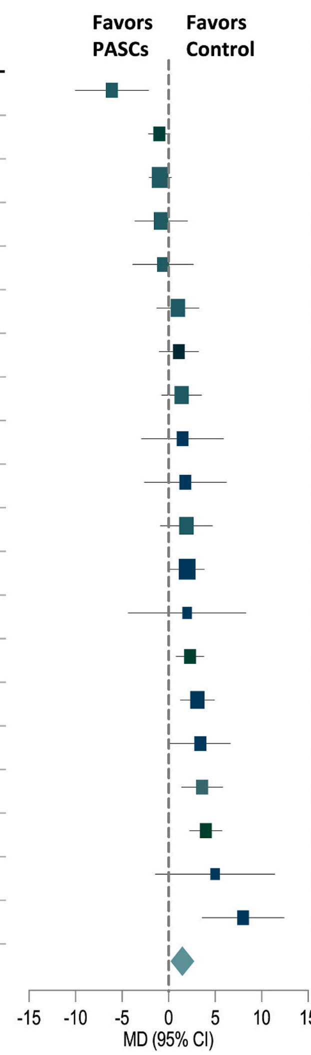


Fig. 4. Forest Plot of VE/VCO_2 before and after Exercise between COVID-19 Survivors and Non-COVID-19 Controls.
Abbreviations: COVID-19, coronavirus disease 2019; PASC, Post-Acute Sequelae of SARS-CoV-2 Infection; VE/VCO_2, VE per unit carbon dioxide production.

difference was observed in fatigue, dyspnea, peak HR, SpO_2, peak VE, exercise duration, cardiac output, and BP in exercise testing (eFigs. 7–14 in the Supplement). On the other hand, HR, SpO_2, BP, and $ETCO_2$ were comparable between COVID-19 survivors and non-COVID-19 controls at rest (eFigs. 15–18 in the Supplement). Interestingly, VE/VCO_2 was the only outcome that altered at rest but remained unchanged in COVID-19 survivors (Fig. 4). Regarding study heterogeneity, high heterogeneity was found among included studies in some of the reported outcomes, such as 6MWT, VO_2max, and physical activity, which may in part be driven by differences in terms of follow-up time, disease severity during SARS-Cov-2 infection, study design, and ethnics.[2]The heterogeneity remained substantial after sensitivity analyses by excluding some of the studies.

3.4. Study quality and publication bias

A summary of the risk of bias in the included studies is available in the eTable 3-5 in the Supplement. Funnel plots for evaluating publication bias are presented in eFig. 19 and eTable 6 in the Supplement. Although publication bias was identified in VO_2max, VE/VCO_2, SpO_2, it does not affect the result after adjusting the "missing data" by using the trim-and-fill method. No asymmetry was detected using funnel plots, Mazumdar's rank correlation test, and Egger's regression test in the other outcomes.

4. Discussion

This systematic review and meta-analysis assessed the evidence of physical exercise-related manifestations of PASC in COVID-19 survivors at least 3 months post-infection. Our results suggest that the manifestations of PASC are underestimated. Many physical exercise-related parameters of aerobic and anaerobic capacity, such as 6MWT, VO_2max, and AT, were found to be impaired in COVID-19 survivors; as determined using exercise testing; these were, however, comparable between COVID-19 survivors and non-COVID-19 controls at rest.

The prevalence of PASC varies among studies worldwide, ranging from 9 % to 81 %.[2] This was mainly attributed to demographic differences and the COVID-19 pandemic severity. Despite the self-reported physical exercise-related manifestations of PASC by COVID-19 survivors, such as post-exertional malaise, post-exertional fatigue, and physical inactivity,[6] a comprehensive picture of the objectively-measured physical exercise-related manifestations of PASC remain unclear. Our results suggested that the prevalence and manifestations of PASC were underestimated since a wide range of manifestations that can only be determined by exercise testing, but not at rest, were largely neglected. More importantly, the physical exercise-related manifestations of PASC considerably affect COVID-19 survivors' lives due to simultaneously impaired aerobic and anaerobic exercise capacity, as well as other manifestations of PASC.[7] This also results in a lower level of physical activity that may slow down the recovery of COVID-19 survivors from PASC and increase the future risk of mortality and a wide array of diseases.[61] Therefore, early diagnosis and treatment of physical exercise-related manifestations of PASC are needed to reduce the burden of PASC and other related diseases.

Physical deconditioning in both the central and peripheral systems after a long period of inactivity has been proposed as one of the key mechanisms underlying exercise intolerance in COVID-19 survivors.[62] Our findings supported physical deconditioning in both aerobic and anaerobic exercise capacities of COVID-19 survivors. However, this physical deconditioning cannot explain the persistent impairments in physical exercise-related parameters after at least 3 months post-infection, and many of them with mild symptoms may resume physical exercise shortly after recovery.[63] In this systematic review, we also identified pulmonary impairments in COVID-19 survivors by exercise testing, which suggested a non-deconditioning mechanism underlying exercise intolerance. More importantly, reconditioning shortly after COVID-19 may exacerbate the PASC.[7] Thus, further studies on the mechanisms of the physical exercise-related manifestations of PASC, in addition to physical deconditioning, are still needed, which may contribute to the diagnosis and treatment of physical exercise-related PASC.

According to the WHO's guidelines on rehabilitation of physical deconditioning and muscle weakness after COVID-19, several interventions are recommended, including early mobilization, education, functional mobility, muscle stretching and strengthening, and physical exercise.[64] Although an early rehabilitation program is beneficial for COVID-19 survivors, the guideline is not specifically designed for the physical exercise-related manifestations of PASC. Our systematic review and meta-analysis results revealed precise parameters of the manifestation, such as O_2 pulse, BR, $ETCO_2$, and peak lactate, that can serve as therapeutic targets and indicators of physical exercise-related PASC. Moreover, we also confirmed that many conventionally used parameters, such as SpO_2, HR, BP, and cardiac output,[65] were not involved in physical exercise-related PASC based on available evidence, which will contribute to the development of treatments for physical exercise-related PASC in future studies. Since there are various exercise-related manifestations of PASC, we recommend that exercise testing should be included when physicians are evaluating symptoms in COVID-19 survivors.[11] Additionally, as the situations of different patients may vary, and they may experience post-exertional malaise, tailored exercise protocols targeting specific manifestations of PASC may be most suitable for this population to minimize the risk of chronic effects and help re-establish pre-COVID-19 health. Similarly, a recently published set of practical recommendations for exercise training in people with long COVID also suggests differentiating exercise procedures based on the severity of post-exertional malaise.[5]

This study has several limitations. We limited our search to articles written in English. In addition, PASC was termed by the WHO as the symptoms that occur in COVID-19 survivors 3 months after the SARS-CoV-2 infection and last for at least 2 months. Although physical exercise-related manifestations of PASC were determined at least 3 months post-SARS-CoV-2 infection in the included studies, the information regarding the duration of these manifestations was often absent. In addition, information about the duration from infection to admission to the study is incomplete in some of the included studies, which only reported the duration from discharge. Thus, we also included a limited volume of studies with COVID-19 survivors at least 2 months after discharge from the hospital. Future research should provide complete information about the lasting duration of symptoms and time from infection, which is essential to define PASC.

5. Conclusion

In addition to the manifestations of PASC at rest, physical exercise-related manifestations were also determined in COVID-19 survivors using exercise testing. These physical exercise-related manifestations of PASC comprise impairments in both aerobic and anaerobic capacity, which result in severe physical dysfunctions. Therefore, we recommend that exercise testing be included in evaluating the manifestations of PASC in COVID-19 survivors. Future studies should further examine the responses of non-exercise manifestations of PASC to physical exercise and therapeutic strategies to alleviate the physical.

Authors' contributions

CZ and XC conceived and designed research; CZ, XC, JC, ZD and KW performed review and meta-analysis; JC, ZD and KW analyzed data; FS and JH interpreted the results; CZ and XC drafted manuscript; CZ, XC, FS and JH edited and revised the manuscript. All author approved final version of manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jesf.2024.06.001.

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