

Post-COVID-19 Outcomes and Exercise Rehabilitation

Benjamin J.R. Buckley, PhD^{1*}, Stephanie L. Harrison, PhD¹, Elnara Fazio-Eynullayeva, MA²,
Paula Underhill³, Ian D. Jones, PhD⁵, Nefyn Williams, PhD⁶, Gregory Y.H. Lip, MD^{1,4,5}

¹Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart &
Chest Hospital, Liverpool, United Kingdom

²TriNetX Inc., Cambridge, MA, United States

³TriNetX Inc., London, United Kingdom

⁴Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University,
Aalborg, Denmark

⁵Liverpool Centre for Cardiovascular Science, Liverpool John Moores University, Liverpool,
United Kingdom

⁶ Department of Primary Care and Mental Health, University of Liverpool, United Kingdom

Manuscript word count 1000

***Corresponding author**

Dr Benjamin Buckley, Liverpool Centre for Cardiovascular Science, University of Liverpool,
William Henry Duncan Building, Liverpool, L7 8TX United Kingdom

Email: Benjamin.Buckley@liverpool.ac.uk.

Phone: +44 (0)151 794 2000

The COVID-19 pandemic has caused global health, social, and economic system challenges. In an effort to try and reduce transmission rates, most countries have varying levels of societal ‘lockdowns’ and social restrictions in place. This creates a unique challenge for the promotion of physical activity and exercise, which we know has profound physical and mental health benefits. Although there was initial promise of increased population *interest* in physical activity and exercise at the beginning of the COVID-19 pandemic,¹ recent large-scale data from over 455,000 people has demonstrated a 27% decrease in average daily steps within 30-days of the pandemic declaration.²

It may therefore be more important now than ever to facilitate physical activity and exercise promotion during and post-COVID-19. Despite, recent collaborative efforts developing post-COVID-19 guidelines for athletes returning to exercise,³ limited evidence is available for the impact of exercise and cardiac rehabilitation (CR) on clinical outcomes post-COVID-19. Secondary prevention through comprehensive CR has been recognised as the most cost-effective intervention to ensure favourable outcomes across a wide spectrum of cardiovascular diseases.⁴ Given there is a high prevalence of cardiovascular disease among patients with COVID-19, and >7% experience COVID-19 induced myocardial injury,⁵ CR following COVID-19 infection warrants investigation. The objective of this study was therefore to compare mortality, hospitalisation, and cardiovascular comorbidity between patients with cardiovascular disease and COVID-19 with and without an electronic medical record (EMR) of CR or exercise programmes.

This retrospective observational study was conducted in October 2020 with anonymised data provided by TriNetX, a global federated health research network with access to EMRs from participating academic medical centres, specialty physician practices, and community hospitals, predominantly in the United States. Patients with COVID-19 were identified via Centers for Disease Control and Prevention (CDC) coding using ICD-10-CM codes, or specific laboratory Logical Observation Identifiers Names and Codes.⁶ All patients were aged ≥18 years with COVID-19 recorded in EMRs between January 20, 2020 (date COVID-19 first confirmed in the US)⁷ and May 26, 2020 (to allow 4-month follow-up). CR was identified from ICD-10-CM codes Z71.82 (Exercise counselling), HCPCS code S9472 (CR program, non-physician provider, per diem), or CPT code 1013171 (Physician or other qualified health care professional services for outpatient CR). Correspondingly, these CR and exercise programme codes were excluded in the propensity score-matched controls. At the time of the search, 33 participating healthcare organisations had data available for patients meeting the study inclusion criteria. Thus, following propensity score matching, the cohort consisted of patients with cardiovascular disease and a diagnosis of COVID-19; who either were referred for CR and exercise

programmes (due to cardiovascular disease) within 3-months of a COVID-19 diagnosis (intervention) or were not referred (control).

Baseline characteristics were compared using chi-squared tests or independent-sample t-tests. Using logistic regression, CR and exercise patients were 1:1 propensity score-matched with controls for age, sex, race, acute myocardial infarction (AMI), heart failure, hypertensive disease, diabetes mellitus, chronic kidney disease, cerebrovascular disease, cardiovascular procedures (e.g. cardiography, echocardiography, cardiac catheterisation, cardiac devices, electrophysiological procedures), and cardiovascular medications (e.g. beta-blockers, antiarrhythmics, diuretics, antilipemic agents, antianginals, calcium channel blockers, ACE inhibitors). These variables were chosen because they are established risk factors for AF and/or mortality or were significantly different between the two cohorts. Logistic regression produced odds ratios (OR) with 95% confidence intervals (CI) for mortality, hospitalisation, AMI, stroke, and heart failure at 4-months following a COVID-19 diagnosis, comparing CR and exercise with propensity score-matched controls. Statistical significance was set at $P < 0.05$.

In total, 400,383 patients with COVID-19 met the inclusion criteria for the control group and 643 patients with COVID-19 met the inclusion criteria for the CR and exercise cohort. Compared to controls, the CR and exercise cohort were generally older, had less females, and more cardiovascular comorbidities (Table 1). Following propensity score-matching, cohorts were well balanced for age, race, sex, comorbidities, cardiovascular medications and cardiovascular procedures ($p > 0.05$; Table 1).

Using the propensity score-matched cohort, and excluding patients with outcomes outside the measurement window, mortality at 4-months from COVID-19 diagnosis was proportionally lower with 1.6% ($n=10$ of 639 patients) in the CR and exercise cohort compared to 6.4% ($n=41$ of 638 patients) in the controls (OR 0.23, 95% CI 0.12-0.47). Re-hospitalisations were also proportionally lower with 15.1% ($n=97$ out of 643 patients) in the CR and exercise cohort compared to 30.8% ($n=198$ out of 643 patients) in the controls (OR 0.4, 95% CI 0.3-0.53). No differences were found for AMI (OR 1, 95% CI 0.42-2.48), stroke (0.95, 95% CI 0.39-2.31), or heart failure (OR 0.96, 95% CI 0.4-2.34).

Several limitations are of note. Firstly, the characterisation of COVID-19, health conditions, and CR and exercise programmes were based on ICD codes from EMRs, and reporting of conditions with ICD codes may vary by patient characteristics and healthcare organisations.⁸ Indeed, we do not know the severity of individual COVID-19 cases, which may have affected the results. However, before propensity score matching, there was no difference in relative mortality between the cohorts. Thus, it may not be illness

97 severity that differentiated patients receiving CR or not within this cohort. We also do not know details
98 of the CR interventions, including whether they were comprehensive, multicomponent or exercise-
99 only, which limits the ability to identify active ‘intervention ingredients.’ Due to closures in many
100 traditional (centre-based) CR programmes, evaluation of different types of CR is needed, particularly
101 frameworks that are adapted to COVID-19 delivery such as ‘cardiac telerehabilitation’.⁹ Another
102 important caveat, an EMR of CR and exercise does not necessarily provide information as to whether
103 a patient attended, the intervention type and dose, or intervention adherence. We could also not
104 determine the influence of attending different healthcare organizations due to data privacy
105 restrictions. Finally, although we were able to match patients for important co-morbidities and
106 demographic factors, residual confounding may present.

107
108 In summary, the present study of over 1200 patients with cardiovascular disease demonstrated that
109 CR and exercise programmes following COVID-19 is associated with significantly lower odds of
110 mortality and re-hospitalisation at 4-months, when compared to propensity score-matched patients
111 without CR or exercise programmes. The provision of exercise rehabilitation for cardiovascular
112 patients following a COVID-19 diagnosis is therefore a promising entity and warrants further
113 investigation.

Disclosures

Benjamin JR Buckley, Stephanie L Harrison, Ian D Jones, and Nefyn Williams: None declared. Elnara Fazio-Eynullayeva and Paula Underhill are employees of TriNetX Inc. Gregory YH Lip: consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo and speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally.

Funding

No specific funding was received for this study. TriNetX Inc. funded the acquisition of the data used.

Authorship

BJRB and GYHL contributed to the conception or design of the work. BJR contributed to the acquisition, analysis, and interpretation of data for the work. BJR drafted the manuscript. SLH, EFE, PU, IGJ, NW, and GYHL critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

References

1. Ding D, del Pozo Cruz B, Green MA, et al. Is the COVID-19 lockdown nudging people to be more active: a big data analysis. *British Journal of Sports Medicine* 2020;54(20):1183. doi: 10.1136/bjsports-2020-102575
2. Tison GH, Avram R, Kuhar P, et al. Worldwide Effect of COVID-19 on Physical Activity: A Descriptive Study. *Annals of Internal Medicine* 2020 doi: 10.7326/M20-2665
3. Bhatia RT, Marwaha S, Malhotra A, et al. Exercise in the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) era: A Question and Answer session with the experts Endorsed by the section of Sports Cardiology & Exercise of the European Association of Preventive Cardiology (EAPC). *Eur J Prev Cardiol* 2020;27(12):1242-51. doi: 10.1177/2047487320930596
4. Ambrosetti M, Abreu A, Corrà U, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol* 2020:2047487320913379. doi: 10.1177/2047487320913379 [published Online First: 2020/04/01]
5. Clerkin KJ, Fried JA, Raikhelkar J, et al. COVID-19 and Cardiovascular Disease. *Circulation* 2020;141(20):1648-55. doi: 10.1161/circulationaha.120.046941 [published Online First: 2020/03/24]
6. Centers for Disease Control and Prevention. ICD-10-CM Official Coding Guidelines - Supplement Coding encounters related to COVID-19 Coronavirus Outbreak 2020 [Available from: <https://www.cdc.gov/nchs/data/icd/ICD-10-CM-Official-Coding-Guidance-Interim-Advice-coronavirus-feb-20-2020.pdf> accessed 8 June 2020 2020.
7. Holshue ML, DeBolt C, Lindquist S, et al. First Case of 2019 Novel Coronavirus in the United States. *The New England journal of medicine* 2020;382(10):929-36. doi: 10.1056/NEJMoa2001191 [published Online First: 2020/02/01]
8. Chong WF, Ding YY, Heng BH. A comparison of comorbidities obtained from hospital administrative data and medical charts in older patients with pneumonia. *BMC Health Serv Res* 2011;11:105-05. doi: 10.1186/1472-6963-11-105
9. Scherrenberg M, Wilhelm M, Hansen D, et al. The future is now: a call for action for cardiac telerehabilitation in the COVID-19 pandemic from the secondary prevention and rehabilitation section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol* 2020:2047487320939671. doi: 10.1177/2047487320939671

Table 1. Baseline characteristics %(n)* of the COVID-19 populations with and without CR and exercise before and after propensity score matching.

	Initial populations			Propensity score matched populations		
	COVID-19 without CR (n=400,383)	COVID-19 with CR (n=643)	P-value	COVID-19 without CR (n=643)	COVID-19 with CR (n=643)	P-value
Age (years); mean (SD)	47.8 (20.2)	59.4 (18.5)	<0.001	60.3 (18.4)	59.4 (18.5)	0.348
Female	57.2 (229,022)	36.7 (236)	<0.001	37.9 (244)	36.7 (236)	0.645
Race ^a						
White	63.1 (252,745)	76.8 (494)	<0.001	76.8 (494)	76.8 (494)	1
Black or African American	17 (68,120)	17.3 (111)	0.867	17.7 (114)	17.3 (111)	0.826
Unknown	16.7 (66,945)	4.2 (27)	<0.001	3.9 (25)	4.2 (27)	0.777
Hypertensive Diseases	6.7 (26,774)	72 (463)	<0.001	53.3 (343)	72 (463)	<0.001
Diabetes Mellitus	21.6 (86,335)	70.5 (453)	<0.001	74.8 (481)	70.5 (453)	0.08
Heart Failure	4.6 (18,513)	38.4 (247)	<0.001	40.9 (263)	38.4 (247)	0.362
Acute Myocardial Infarction	1.3 (5,016)	35.9 (231)	<0.001	34.5 (222)	35.9 (231)	0.599
Chronic Kidney Disease	9.9 (39,515)	33.1 (213)	<0.001	33.7 (217)	33.1 (213)	0.813
Cerebrovascular Diseases	3.4 (13,784)	18.5 (119)	<0.001	18.1 (117)	18.5 (119)	0.829
Cardiovascular Procedures ^b	5.2 (20,806)	18.5 (119)	<0.001	18.2 (117)	18.5 (119)	0.885
Cardiovascular Medications ^c	38.3 (153,191)	90.7 (583)	<0.001	91 (585)	90.7 (583)	0.847

*Values are % (n) unless otherwise stated. Baseline characteristics were compared using a chi-squared test for categorical variables and an independent-sample t-test for continuous variables. ^aData are taken from structured fields in the electronic medical record systems of the participating healthcare organizations, therefore, there may be regional or country-specific differences in how race categories are defined.

^bCardiovascular procedures include cardiography, echocardiography, catheterization, cardiac devices, electrophysiological procedures. ^cCardiovascular medications include beta-blockers, antiarrhythmics, diuretics, antilipemic agents, antianginals, calcium channel blockers, ACE inhibitors.

CR; cardiac rehabilitation and exercise programmes, SD; standard deviation.