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ORIGINAL ARTICLE

Associations between symptoms and functional capacity in patients after COVID-19 infection and community controls

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Key words
long COVID, exercise capacity, echocardiography, cardiorespiratory fitness, exercise training.

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Abstract

Background: Post-acute sequelae of COVID-19 (PASC or 'long COVID') reflect ongoing symptoms, but these are non-specific and common in the wider community. Few reports of PASC have been compared with a control group.
Aims: To compare symptoms and objective impairment of functional capacity in patients with previous COVID-19 infection with uninfected community controls.
Methods: In this community-based, cross-sectional study of functional capacity, 562 patients from Western Melbourne who had recovered from COVID-19 infections in 2021 and 2022 were compared with controls from the same community and tested for functional capacity pre-COVID-19. Functional impairment (<85% of the predicted response) was assessed using the Duke Activity Status Index (DASI) and 6-min walk distance (6MWD) test. A subgroup underwent cardiopulmonary exercise testing before and after exercise training.
Results: Of 562 respondents (age 54 ± 12 years, 69% women), 389 were symptomatic. Functional impairment (<85% predicted metabolic equivalent of tasks) was documented by DASI in 149 participants (27%), and abnormal 6MWD (<85% predicted) was observed in 14% of the symptomatic participants. Despite fewer risk factors and younger age, patients with COVID-19 had lower functional capacity by 6MWD ($P < 0.001$) and more depression ($P < 0.001$) than controls. In a pilot group of seven participants (age 58 ± 12 years, two women, VO_2 18.9 ± 5.7 mL/kg/min), repeat testing after exercise training showed a 20% increase in peak workload.
Conclusions: Although most participants (69%) had symptoms consistent with long COVID, significant subjective functional impairment was documented in 27% and objective functional impairment in 14%. An exercise training programme might be beneficial for appropriately selected patients.

Introduction

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has brought an unprecedented crisis to public health globally and is still impacting millions of people. According to World Health Organization (WHO) data in March 2023, there have been approximately 758 million confirmed COVID-19 cases and 6.8 million deaths worldwide, with over 11 million confirmed cases and approximately 20 000 deaths in Australia.[1] There is increasing evidence that many patients with COVID-19 could experience a wide range of post-acute sequelae, including significant cardiovascular complications.[2,3]

Post-viral symptoms are common (>70%) in the first month after COVID-19 infection.[4] Fewer patients describe continuing symptoms for 3 months – the arbitrary cut-point chosen by the WHO for the definition of post-acute sequelae of COVID-19 (PASC, or 'long COVID').[4] Although the incidence of this problem ranges from 8% to 12%, infection of ~758 million people with COVID-19[1] means that there is a very large cohort of patients with this

Conflict of interest: None.

condition. Female sex, middle age, the presence of ≥2 comorbidities and the intensity of the original infection are associated with the risk of developing long COVID,[5] but community-based patients with milder COVID-19 are far from exempt,[6] although the frequency and intensity of long-term symptoms seem to be attenuated in vaccinated individuals.[6,7] Long COVID is a heterogeneous condition,[8] with clusters caused by autonomic dysfunction,[9] immune activation, endotheliopathy[10] and neuropsychiatric symptoms. The constellation of symptoms – of which debilitating fatigue is a central component[11,12] – includes exercise intolerance and functional impairment. It seems likely that the association of reduced functional capacity with depression reflects a common response to ongoing illness, although fatigue may be a symptom of depression. Myocardial injury after COVID-19 infection – evidenced by biomarkers (e.g. cardiac troponin (Tn))[13] and imaging evidence of inflammation and overt dysfunction by cardiac magnetic resonance imaging[14] – may be important. Many of these patients have been unwell for months, so there may also be an element of deconditioning. Understanding the long-COVID phenotypes may better identify patients likely to be responsive to interventions, including exercise training.[15]

This study sought to better understand the association of long-COVID symptoms and functional impairment in a community-dwelling population who have recovered from the initial illness. It was hypothesised that long-COVID participants would show heterogeneity of functional capacity, but this would be less than community controls. Accordingly, this study used a cohort of COVID-19 survivors with and without symptoms to establish the prevalence of reduced functional capacity and the potential responsiveness to rehabilitation.

Methods

Participants

In response to advertising on social media, 562 respondents from Western Melbourne who had COVID-19 infection in 2021–2022 were recruited into the PERCEIVE study and compared with community-based subjects who underwent the same tests before the pandemic (2019 and before). For controls, this study included 979 participants (aged 70 ± 4 years) who had been recruited into two previous community-based studies (VicELF and TasELF)[16,17] before the pandemic, and therefore exclude COVID-19 with a certainty that is not achievable with current control groups.[18] In both groups, patients with known valvular stenosis or regurgitation of moderate or greater severity, history of previous heart failure, mobility impairment that would impact participants' ability to perform exercise or life expectancy <12 months were excluded. The study was approved by the Alfred Human Research Ethics Committee (72455), and all participants gave informed consent.

Study design

Because of lockdowns during the pandemic, the screening process was designed to be initiated online. Patients with a Duke Activity Status Index (DASI) score less than normal for their age or those with a high-sensitivity Tn >15 ng/L were invited to attend a clinic to assess 6-min walk distance (6MWD). Cardiopulmonary exercise tests (CPETs) were performed in participants with reduced functional capacity or an abnormal Tn.

Clinical characteristics

Baseline data were collected through validated methods, including self-administered questionnaires, semi-structured interviews and clinical assessment. The demographic profile included age, sex, marital status, social support, income, education, ethnicity and language. The clinical profile included the presence of cardiovascular risk factors, comorbid disease and medical therapy, and past/concurrent cardiac and non-cardiac disease states, including history of cardiovascular risk factors, known coronary artery disease, valvular heart disease and functional class. Validated questionnaires were used to assess sociodemographic, clinical status, depression (PHQ-9)[19] and overall health and well-being (AQoL-8D).[20] Routine biochemistry (Cobase 601, Roche Diagnostics, North Ryde, NSW) included assessment of high-sensitivity Tn, identified as abnormal (>15 ng/L) and borderline (5–15 ng/L).

Functional capacity

6MWD[21] and DASI[22] were obtained to assess functional capacity in both post-COVID-19 patients and controls. Both have been previously validated against peak oxygen uptake and associated with outcome.[23,24] DASI was performed as a self-administered questionnaire; an abnormal test was defined if predicted metabolic equivalent of tasks (METS) were <85% of age- and sex-defined normative values.[25] A 6MWD was performed in line with the American Thoracic Society guidelines.[21] Because age is a significant determinant of 6MWD, a percentage of the expected normal findings was used in this study[26] (<85% of predicted was considered abnormal).

Peak $\dot{V}O_2$ was determined from breath-by-breath gas analysis (Vyntus or MedGraphics CPX/D) following a standardised protocol.[27] Heart rate (HR) and blood

pressure were measured at baseline, throughout exercise and in recovery.

Exercise training

Post-COVID-19 participants with reduced exercise capacity were offered the opportunity to participate in an exercise training programme. The aim of this exercise intervention was to help participants manage their condition while assisting them in restoring their optimal physical function. This was achieved by engaging in a structured exercise training programme prescribed by an exercise physiologist (EP) and delivered through different modalities depending on the participant's preference.

Participants completed two supervised sessions/week (either in person or online). Continuous exercise sessions were completed on a treadmill, cycle ergometer or as an outdoor walk at moderate intensity of rated perceived exertion (RPE) of 11–13/20 and HR 55–70% of maximum (informed from the participants' baseline CPET). Similarly, interval-based aerobic activity was performed at high intensity (RPE >16/20, HR max >90%). Generally, this led to most participants performing 30 (or more) min of continuous aerobic activity by the end of the programme. The strength component involved six to eight exercises (a combination of bodyweight, free-weight or resistance-bands) with the goal of two sets of 15 repetitions by the end of the programme.

Statistical analysis

This study initially sought to recruit 300 post-COVID-19 participants, with the expectation that reduced functional capacity would be present in 50% of patients.[28] However, as the frequency of reduced functional capacity was lower than expected (27%), it required 562 participants to identify the number of initially planned participants with reduced functional capacity ($n = 149$). This sample size provided greater than sufficient power to detect a significant difference in functional capacity between the post-COVID-19 and control cohorts. There were no missing data for the primary endpoint; all participants proceeding to other tests are described.

Categorical variables were reported as numbers and percentages and continuous variables as either mean with standard deviation or median with interquartile range. One-way analysis of variance was used to determine statistical differences among groups of participants. Logistic regression was used to estimate the associations of variables with binary outcomes. C-statistics and areas under the curve (AUCs) were used to compare discriminatory power among predictive models. Statistics were performed using standard software STATA 17 (StataCorp, College Station, TX, USA). A P value <0.05 was used to define statistical significance in this study.

Post-COVID-19 participants were matched to those in the control cohort using a previously published propensity-matching method.[29] Because of the age differences between the two samples, two propensity scores were calculated, one based on sex and cardiovascular risk factors and the other based on age and sex. When matching based on sex and risk factors, the majority of post-COVID-19 participants (542/562, 96%) were matched 1:1 to their controls. When matching based on age and sex, only 21% (120/562) of the COVID-19 participants could be matched. Findings from both of these two propensity-matching scores are shown for comparison.

Results

Clinical status of post-COVID-19 patients

Out of 562 post-COVID-19 patients who responded to invitations to participate, 55 (10%) were hospitalised for their initial infection. At the time of testing (>1 month after COVID), 173 (31%) were asymptomatic, 65 (11%) were symptomatic for <90 days after infection and 324 (58%) had symptoms for >90 days.

Details of viral variants were not available. However, as Omicron became the dominant COVID-19 variant in Australia in December 2021, this date was used to separate those with expected Omicron and those with earlier variants. The group with expected Omicron was generally less symptomatic than the remainder (Table 1), especially dyspnoea, but were more likely to have cough/sneeze/running nose. Overall, 80% (447/562) of the study group were vaccinated at the time of their COVID-19 infection, with 77% (433/562) having at least two doses. None of the participants received antiviral therapy.

Ongoing symptoms were significantly associated with depressive symptoms, with a relatively large difference in PHQ-9 scores between patients with and without long-COVID symptoms. Most patients with ongoing sleep disturbance, flu-like symptoms, palpitations and chest pain had scores associated with moderate or severe depression (Appendix Table 1). Moderate or severe depression was associated with 14.43-fold (95% confidence interval (CI): 8.50–24.50) greater odds of having DASI-METS <85% predicted and 5.05-fold (95% CI: 1.98–12.84) greater odds of having <85% predicted 6MWD. In a logistic model (AUC: 0.87), moderate to severe depression was associated with sleep disturbance (OR: 4.77 (95% CI: 2.29–9.91)), fatigue (OR: 8.67 (95% CI: 3.48–21.58)), dyspnoea (OR: 4.77 (95% CI: 2.29–9.91)), chest pain (OR: 2.95 (95% CI: 1.49–5.87)) and rash (OR: 2.98 (95% CI: 1.43–6.19)).

Table 1 Differences in long-COVID symptoms according to expected COVID-19 variant

		COVID-19 variant		
	N (%)	Not Omicron ($n = 322$)	Likely Omicron ($n = 240$)	*P* value
Fever	5 (1%)	3 (0.9%)	2 (0.8%)	0.90
Shortness of breath/dyspnoea	170 (30%)	112 (34.8%)	58 (24.2%)	0.006
Fatigue	278 (49%)	159 (49.4%)	119 (49.5%)	0.96
Chest pain	82 (14%)	54 (16.8%)	28 (11.7%)	0.09
Cough/sneeze/running nose	109 (19%)	46 (14.3%)	63 (26.2%)	<0.001
Flu-like symptoms	59 (10%)	36 (11.1%)	23 (9.6%)	0.54
Palpitation	74 (13%)	49 (15.2%)	25 (10.4%)	0.09
Diarrhoea	15 (3%)	12 (3.7%)	3 (1.2%)	0.07
Loss of smell	44 (8%)	31 (9.6%)	13 (5.4%)	0.066
Loss of taste	43 (8%)	25 (7.8%)	18 (7.5%)	0.91
Loss of appetite	19 (3%)	10 (3.1%)	9 (3.7%)	0.67
Abdominal pain	17 (3%)	13 (4.0%)	4 (1.7%)	0.11
Insomnia	61 (11%)	34 (10.5%)	27 (11.2%)	0.79
Skin rash or other skin condition	19 (3%)	15 (4.6%)	4 (1.7%)	0.05
Other symptoms	88 (16%)	61 (18.9%)	27 (11.2%)	0.013
Any long-COVID symptoms	389 (69.2%)	220 (68.3%)	169 (70.4%)	0.59

Functional impairment

Based on the DASI, 149 (27%) had an estimated exercise capacity <85% predicted METS. Functional impairment was significantly associated with the presence of almost all symptoms, with the exception of fever and disturbed sense of smell (Appendix Table 2). Dyspnoea, fatigue and flu-like symptoms were among the strongest associations of subjective functional impairment (Table 2).

Out of 114 with symptoms of significantly impaired functional capacity and who attended for functional assessment, 31 (27%) had a reduction of the 6MWD to <85% age-predicted. In contrast, only three (2%) of 158 with preserved functional capacity had a below-predicted 6MWD (Fig. 1). Conversely, 6MWD was >85% predicted in about 80% of people with reduced functional capacity based on DASI. Dyspnoea and fatigue were correlates of symptoms with 6MWD (Appendix Table 3), but although flu-like symptoms (OR: 3.44 (95% CI: 1.44–8.24)), palpitations (OR: 3.70 (95% CI: 1.63–8.39)) and insomnia (OR: 2.78 (95% CI: 1.14–6.76)) were associated with objective evidence of reduced functional capacity, the prediction was modest (AUC: 0.72, Appendix Table 4).

Table 2 Association of impaired functional capacity (reduced DASI score) with persistent COVID symptoms

	OR (95% CI)	AUC (95% CI)
Fever	9.58 (1.06–86.41)	0.51 (0.50–0.52)
Shortness of breath/dyspnoea	4.35 (2.95–6.42)	0.66 (0.62–0.70)
Fatigue	5.69 (3.75–8.61)	0.70 (0.66–0.74)
Chest pain	4.50 (2.77–7.33)	0.60 (0.57–0.64)
Cough/sneeze/running nose	2.40 (1.56–3.70)	0.57 (0.53–0.61)
Flu-like symptoms	8.96 (4.82–16.67)	0.61 (0.58–0.65)
Palpitation	4.30 (2.59–7.15)	0.59 (0.56–0.63)
Diarrhoea	10.02 (1.79–36.01)	0.53 (0.51–0.55)
Loss of smell	1.70 (0.90–3.19)	0.52 (0.49–0.55)
Loss of taste	3.29 (1.75–6.19)	0.55 (0.52–0.57)
Loss of appetite	22.07 (5.04–96.66)	0.55 (0.52–0.57)
Abdominal pain	8.18 (2.62–25.47)	0.53 (0.51–0.55)
Insomnia	4.02 (2.33–6.96)	0.57 (0.54–0.61)
Skin rash/other conditions	3.38 (1.33–8.56)	0.52 (0.50–0.54)
Other symptoms	2.13 (1.33–3.39)	0.55 (0.52–0.59)
Any long-COVID symptoms	4.70 (2.82–7.81)	0.63 (0.60–0.67)

AUC, area under the curve; DASI, Duke Activity Status Index; OR, odds ratio.

Of 27 symptomatic patients with evidence of functional impairment by 6MWD who underwent CPET, the average peak VO_2 was 20 ± 5 mL/min/kg (75 ± 16% of predicted). The 6MWD results were not a good indicator of peakVO_2 ($r = 0.34$); 13 patients with 6MWD ≤85% predicted had average peak VO_2 of 20 ± 3 mL/min/kg, compared with 19 ± 6 mL/min/kg in those with a normal 6MWD ($P = 0.80$). These values represent 71 ± 20% and 78 ± 8% of predicted peak VO_2 respectively.

Troponin levels

Tn-T was elevated (>15 ng/L) in 12 out of 263 participants (5%) and borderline (5–15 ng/L) in 147 (56%). Levels of Tn-T were not associated with symptoms. There were no differences in those with normal and impaired 6MWD (6.6 ± 4.5 vs 6.0 ± 4.2 ng/L, $P = 0.44$) or normal and impaired peak VO_2 (12.8 ± 5.1 vs 12.2 ± 11.1 ng/L, $P = 0.88$). Elevated Tn levels were not associated

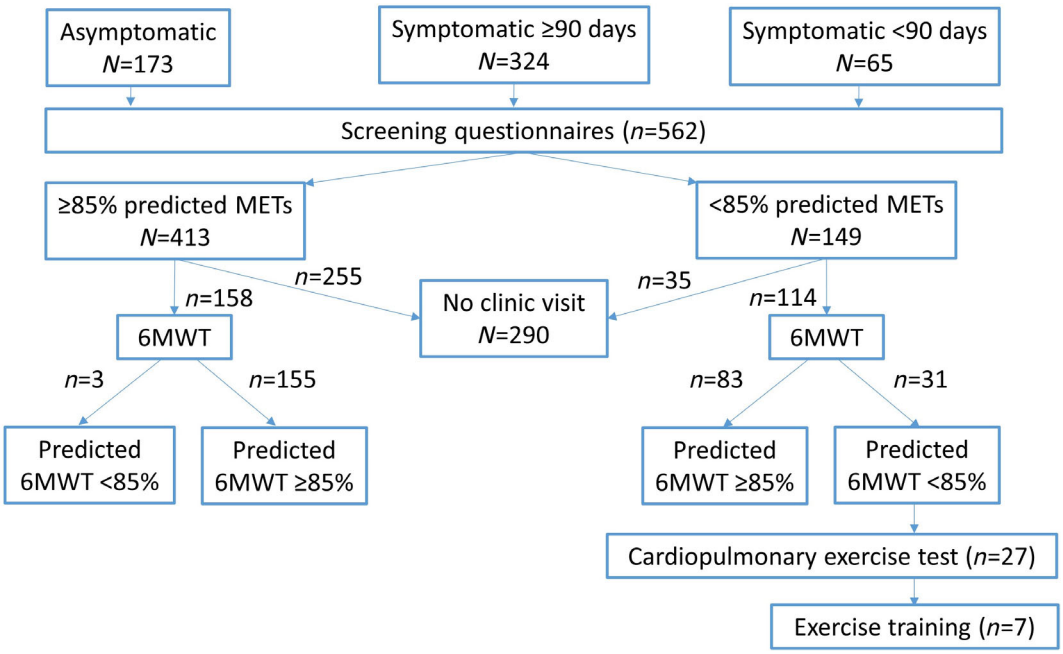

Figure 1 Subjective and objective impairment of functional capacity after COVID.

Table 3 Differences in clinical features and functional capacity in patients with and without COVID. These data compare participants recovered from COVID-19 (PERCEIVE study) with patients from the same community with cardiac risk factors before the pandemic (VicELF and TasELF trials) before and after propensity matching for risk factors and demographics

	Before matching			Propensity matched for risk factors (RFs)†			Propensity match for age and sex		
Variables	Vic/TasELF, *N* = 979	PERCEIVE, *N* = 562	*P* value	Vic/TasELF, *N* = 542	PERCEIVE, *N* = 542	*P* value	Vic/TasELF, *N* = 120	PERCEIVE, *N* = 120	*P* value
Demographic									
Age	70.9 ± 4.7	54.3 ± 11.8	<0.001	68.8 ± 1.9	54.1 ± 11.8	<0.001	68.9 ± 3.7	68.8 ± 3.7	0.93
Male	46%	30%	<0.001	30%	30%	1.0	31%	35%	0.49
Comorbidity									
T2DM	44%	6%	<0.001	6%	6%	1.0	27.5%	8.8%	<0.001
HTN	82%	21%	<0.001	20%	20%	1.0	93.3%	41.2%	<0.001
Obesity	51%	19%	<0.001	19%	19%	1.0	76.7%	20.7%	<0.001
Functional capacity									
DASI score	42.7 ± 11.5	42.4 ± 15.4	0.65	43.7 ± 11.5	42.8 ± 15.1	0.31	45.4 ± 11.3	37.2 ± 13.9	<0.001
METS	8.0 ± 1.4	7.9 ± 1.9	0.65	8.1 ± 1.4	8.0 ± 1.9	0.31	8.3 ± 1.4	7.3 ± 1.7	<0.001
<85% predicted METS	4%	26%	<0.001	9%	26%	<0.001	0%	12.5%	<0.001
6MWD‡	459 ± 89	567 ± 98	<0.001	427 ± 66	567 ± 97	<0.001	445 ± 67	508 ± 90	<0.001
<85% predicted 6MWD‡	15%	12%	0.32	38%	13%	<0.001	10.8%	4.1%	0.10
Mental health									
PHQ-9 score	2.0 ± 3.5	5.6 ± 5.3	<0.001	1.1 ± 0.8	5.5 ± 5.3	<0.001	1.4 ± 1.9	4.2 ± 4.5	<0.001
Moderate/severe depression	5%	21%	<0.001	0%	20%	<0.001	0%	11%	<0.001

†RFs used for propensity matching included sex, type-2 diabetes mellitus, hypertension and obesity.
‡Data were only available in 260 matched participants in PERCEIVE.
DASI, Duke Activity Status Index; GLS, global longitudinal strain; HTN, hypertension; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; METS, maximum metabolic equivalent of tasks; PHQ-9, Patient Health Questionnaire 9; T2DM, type-2 diabetes mellitus; 6MWD, 6-min walk distance.

with long-COVID symptoms or reduced functional capacity.

Clinical features and functional capacity with and without COVID-19

The same functional features were obtained in the non-COVID controls (Table 3). The PHQ-9 score and prevalence of moderate and severe depression were significantly worse in the COVID-19 group, irrespective of how patients were matched (Table 3).

Significant differences in functional capacity between the COVID-19 participants and their controls were only revealed when the groups were matched by age and sex – in other words, the younger age of the COVID-19 patients masked their functional compromise. Functional impairment was present in COVID-19 participants regardless of the presence of long-COVID symptoms. Both functional impairment and depression were more severe and prevalent in COVID-19 participants with long COVID compared with those without long COVID (Appendix Table 5).

Exercise response

A pilot group of seven participants (age 58 ± 12 years, two women) with reduced functional capacity (estimated METS by DASI 73 ± 12% predicted, peak VO_2 18.9 ± 5.7 mL/kg/min) were reassessed after training (Table 4). Participants completed on average 13.4 supervised sessions (range 5–24). At follow-up testing, all this group showed an increased peak workload (by 20%, $P = 0.008$) and all but one showed an increase in peak VO_2 (by 7.3%, $P = 0.057$).

Table 4 Exercise training response. Haemodynamic and cardiopulmonary responses to exercise training over 31 ± 13 weeks

	Baseline	Follow-up	Delta	*P*
Rest HR, bpm	74 ± 10	76 ± 13	−3 ± 6	0.74
Rest SBP, mmHg	150 ± 19	130 ± 10	−12 ± 18	0.036
Rest DBP, mmHg	89 ± 11	87 ± 6	0 ± 11	0.28
Peak SBP, mmHg	217 ± 23	201 ± 26	−14 ± 19	0.253
Peak DBP, mmHg	110 ± 90	96 ± 8	−30 ± 35	0.04
Peak HR, bpm	153 ± 14	156 ± 21	11 ± 18	0.52
Peak VO_2 (mL/kg/min)	18.9 ± 5.7	20.3 ± 6.2	1.5 ± 1.7	0.0.057
Peak VO_2 (L/min)	1.84 ± 0.62	1.95 ± 0.68	0.11 ± 0.14	0.072
RER	1.23 ± 0.08	1.27 ± 0.10	0.01 ± 0.06	0.33
Peak workload (W)	137 ± 55	160 ± 56	26 ± 13	0.008

Values are mean ± SD. DBP, diastolic blood pressure; HR, heart rate; RER, respiratory exchange ratio; SBP, systolic blood pressure.

Discussion

This study emphasises the presence of reduced exercise capacity in some patients with long-COVID symptoms, with the group having a lower exercise tolerance than people from the same community, studied before the COVID-19 pandemic. The results show that depression may be associated with persistent post-COVID-19 symptoms and reduced functional capacity.

Functional reserve in long COVID

The objective definition of impaired functional reserve can be challenging as it requires expensive equipment and specialist expertise to perform the testing. CPET is the reference standard for this purpose, but this is difficult to access in the community. In a meta-analysis of nine published studies that allowed comparison of expired gas analysis (823 people, of whom 464 had symptoms of PASC),[30] Durstenfeld documented a reduction of peak VO_2 of −4.9 (95% CI: −6.4 to −3.4) mL/kg/min among those with symptoms. The common causes of the reduced peak VO_2 were deconditioning, abnormal oxygen extraction, dysfunctional breathing and chronotropic incompetence. In a prospective, multicentre cohort study of 180 previously hospitalised COVID-19 patients who underwent CPET at 3 and 12 months after discharge, there was a significant (5%) increase in per cent peak VO_2 between visits, to the extent that exercise capacity was normal in 77% at 12 months.[31]

In this study, DASI[22] was used as the primary screening test for impaired functional capacity. Although this score is based on the patients' subjective assessment of their functional capacity, it was previously shown to correlate well with measured peak VO_2. Despite the younger age of the post-COVID-19 population than the control group, the former had a significantly lower functional capacity than the controls, even when matched for their risk factor status. The 6MWD is an alternative approach to measuring exercise capacity in the community,[21] without the need for exercise equipment. Possibly because of a ceiling effect in younger individuals, 6MWD showed some discrepancy with DASI-based assessment of functional capacity (and VO_2) and was not associated with the expected long-COVID symptoms.[32] These findings suggest that screening patients with DASI may be sufficient to select those who would be most likely to have abnormal findings at formal exercise testing.

Limitations

The experience of COVID-19 has been different in Australia than elsewhere in the world (mainly Omicron

infections in a mainly vaccinated population), so it is possible that these findings may not be valid in another environment. A historical control cohort was selected in order to ensure that control patients were unexposed to COVID-19, but there were differences between the current and control groups. Although the propensity matching could remove most of the potential confounding related to differences in age, sex and cardiovascular risk factors between the two cohorts, the historical controls did not experience the intense lockdowns experienced during the study period. This residual difference between the two groups might have impacted our findings. However, findings from this study show significant differences in functional capacity and mental health between the COVID-19 participants and their controls and more severe functional impairment and depression among COVID-19 survivors with long COVID compared with COVID-19 survivors without long COVID. These findings suggest that functional impairment and depression observed in our study were likely a consequence of COVID-19 and long COVID rather than the lockdown effects. The performance of exercise training in only seven participants was obtained to understand the feasibility, and we would not use this to provide a recommendation for this intervention in people with long COVID. We are currently performing a randomised controlled trial to determine the benefits of exercise training in people with long COVID.

Conclusion

The results of this study show impairment of both objective and subjective functional capacity in a proportion of people infected with COVID-19 which appeared to be exacerbated in those with long COVID, suggesting that physical deconditioning – presumably because of weeks or months of inactivity – may be causative in some. The high prevalence of depression that was associated with COVID-19 and long COVID was a concern that might need public health intervention. Future longitudinal studies are required to determine the causal relationship between long COVID and these adverse outcomes.

Clinical implications

The standard approach to long-COVID symptoms has been the provision of supportive care.[8,33] Although limited preliminary data support the notion that exercise training may improve functional capacity[34] and reduce symptoms, there is no consensus as to the benefits of this in this setting.[35] Caution needs to be applied to patient selection, as there is an overlap between long COVID and chronic fatigue syndrome,[36] and exercise may be detrimental in the latter.[37] Nonetheless, a randomised trial to test the efficacy of exercise in appropriately selected patients seems warranted.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Data S1. Supplementary tables.