

# Cardiopulmonary, functional, cognitive and mental health outcomes post COVID, across the range of severity of acute illness, in a physically active working age population

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## Research Article

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# Abstract

**Objectives:** To investigate cardiopulmonary, functional, cognitive, and mental health post-COVID-19 outcomes in a young, physically active working-age population, across the spectrum of acute COVID-19 severity.

**Methods:** Observational cohort study of 4 groups; hospitalised, community illness with on-going symptoms (community-symptomatic), community illness now recovered (community-recovered) and controls. Participants underwent extensive clinical assessment involving cardiopulmonary imaging, submaximal and maximal exercise testing, pulmonary function, cognitive assessment, blood tests, electrocardiogram and questionnaires on mental health and physical function.

**Results:** 113 participants (aged  $39 \pm 9$  and 86% male) were recruited into four groups, Hospitalised (n=35), community-symptomatic (n=34), community-recovered (n=18) and control (n=26), at  $159 \pm 72$  days following acute illness. Hospitalised and community-symptomatic groups were older, with a higher body mass index, and worse mental health, fatigue, and quality of life scores. Hospitalised and community-symptomatic participants also performed less well on sub-maximal and maximal exercise testing. Hospitalised individuals had impaired ventilatory efficiency (higher  $VE/\dot{V}CO_2$  slope), achieved less work at the anaerobic threshold and at peak than other groups and had a significantly reduced forced vital capacity. Clinically significant abnormal cardiopulmonary imaging findings were present in 6% of hospitalised participants. Those who recovered from COVID-19 had no significant differences when compared with controls.

**Conclusion:** Recovered individuals who suffered mild-moderate COVID-19 do not differ from an age, sex and job-role matched control population. Individuals who were hospitalised or continue to suffer symptoms require a specific, comprehensive assessment prior to a return to full physical activity.

## Key message

This study demonstrates that, in a physically active, working-age population, those who are symptomatically recovered from mild-moderate COVID-19 do not differ in any parameter from a control group of uninfected individuals matched for age, sex and job-role.

Those who were hospitalised and community-managed patients with ongoing symptoms have worse outcomes in terms of cardiopulmonary imaging findings, functional capacity, and mental health status compared to both community-recovered and control groups.

Individuals whose occupation or recreation requires high intensity physical activity, who have either had severe disease requiring hospitalisation, or are suffering persistent symptoms beyond 12 weeks, require specific, focussed assessment prior to a return to full physical activity.

## Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) continues to cause significant mortality and morbidity, with over 270 million confirmed cases, and 5 million deaths, of coronavirus disease 2019 (COVID-19) globally..(1) Approximately 80% of SARS-CoV-2 cases are asymptomatic or mild, with many patients recovering within 2–4 weeks.(2) However, COVID-19 also causes prolonged illness, with some individuals experiencing persistent symptoms for months, including shortness of breath (SoB), fatigue and mood disturbance.(3-6) The National Institute for Health and Care Excellence (NICE) have adopted time based definitions for post COVID illness: after four weeks, 'ongoing symptomatic COVID-19', and beyond 12 weeks, 'post-COVID-19 syndrome'. An estimated 1.2 million people in the UK (population: 66 million) have ongoing symptoms at  $\geq 4$  weeks.(7)

The mean age of post-COVID-19 syndrome sufferers is  $\sim 40$  years, whilst approximately 20% of previously healthy 18-35 year olds report ongoing symptoms at 14-to-21 days, implying the majority of negatively affected individuals are in the working population.(8, 9) This has consequences for return to work and economic recovery. Initial studies found the severity and duration of the acute COVID-19 increased the risk of chronicity, but this is now challenged.(10, 11) The majority of studies investigating post-COVID-19 syndrome have focussed on hospitalised patients, with few analysing non-severe cases, and fewer still utilising a control population(3, 5, 12-21). Ongoing symptoms consistently include SoB, fatigue, pain, mood disorder and perceived cognitive impairment.(3, 13) Cross-sectional cardiopulmonary imaging abnormalities, including lung fibrosis and myocardial inflammation (22, 23) and functional limitation have been recorded.(24-26)

An inability to fully recover from COVID-19 has a high impact on two diverse groups. Professional athletes and front-line emergency services (e.g., police, firefighters, paramedics, military) are exposed to high volume/intensity exercise as a core component of their role, often under challenging environmental conditions. Any enduring pathology may impair their cognitive judgement and return to high-end physical function. Alongside a specifically commissioned clinical service,(27) the Military COVID-19 Observational Outcome in a Viral Infectious Disease (M-COVID) study was developed to describe the effects of SARS-CoV-2 on the UK Armed Forces. M-COVID allowed detailed characterisation of cardiopulmonary pathology and functional, neurocognitive and mental health status across three cohorts: hospitalised illness (H), community illness with on-going symptoms (community-symptomatic, CS) and community illness now recovered (community-recovered, CR), compared to an age, gender and job-role matched control population (CON).

## **Methods**

### **Study Design**

Prospective observational cohort study. Ethically approved by the Ministry of Defence research ethic committee in July 2020 (1061/MODREC/20).

### **Patient and public involvement**

Multiple focus groups were held at the Defence Medical Rehabilitation Centre (DMRC) Stanford Hall with potential participants during the study design phase. Iterative feedback was gained on the patient information leaflet, study concept and design, and study visit details.

## Setting

Clinical assessments occurred over three days. Two days at DMRC for cardiopulmonary exercise testing (CPET), functional tests, cognitive assessment, spirometry, blood samples and patient reported outcome measures. The third day was at Oxford University Hospital (OUH) NHS Foundation Trust for cardiopulmonary imaging and additional pulmonary function testing (Figure 1)

## Participants

113 participants were categorised into 1 of 4 groups; hospitalised (n=35); community-symptomatic (n=34); community-recovered (n=18), and; control (n=26). Exposed participants were recruited via the clinical pathway.(27) Severity categories were determined pragmatically, with all hospitalised participants requiring supplementary oxygen. Recovered and control participants were recruited from military units and key occupational groups. All controls were nucleocapsid antibody negative. Two senior consultants clinically adjudicated all volunteers who met the eligibility criteria (Online Resource 1) based on positive SARS-CoV-2 antigen testing, history, blood tests and imaging.

## Determining Recovery status

Non-recovery was defined as the continued presence of one or more post-COVID-19 symptoms at recruitment (Table 1).

**Table 1:** Prevalence of symptoms across all groups

Symptom	H	CS	CR	CON
Any Shortness of Breath	63%	71%	0%	0%
Fatigue	54%	68%	0%	4%
Chest Pain	20%	35%	0%	0%
Exercise Intolerance	20%	35%	0%	0%
Joint Pain	26%	15%	0%	0%
Loss of Smell	9%	21%	0%	0%

Abbreviation: H, hospitalised illness; CS, community illness with on-going symptoms (community-symptomatic), CR, community illness now recovered (community-recovered; CON age, gender and job-role matched control population.

## Baseline observations

Heart rate (HR), blood pressure (BP), temperature, and peripheral oxyhaemoglobin saturations (SpO<sub>2</sub>) were acquired by an IPM 8 Mindray Patient Monitor (Mindray UK Ltd, Huntingdon, UK).

## **Venous blood sampling**

Samples were taken for full blood count, liver function, urea and electrolytes, C-reactive protein, creatinine kinase, thyroid function, ferritin and iron studies, vitamin D, and antibodies (spike and nucleocapsid).

## **Cardiopulmonary functional testing**

### *Six-minute walk test (6MWT)*

6MWTs were performed in a gymnasium using standardised guidelines (28), with pre-test body composition recorded (stature, body mass, hip and waist circumference). A pulse oximeter (Nonin Onyx Vantage 9590, Minnesota, USA) was used to measure HR and SpO<sub>2</sub>, with participant's rate of perceived exertion (RPE, 6 to 20)(29) and SoB (0 to 10)(30) recorded, pre- and post-test.

### *Spirometry and pulmonary function test*

Standing spirometry assessments (MicroMedical MicroLab 3500, CA, USA) were taken to measure forced vital capacity (FVC) and forced expiratory volume in the first second of expiration (FEV<sub>1</sub>).(31) The diffusing capacity of the lungs for carbon monoxide (DLCO) was measured over a 10-second breath hold, using methane as a tracer gas.

### *Cardiopulmonary Exercise Testing (CPET)*

CPET was conducted in a temperature-controlled exercise laboratory on an electromagnetically braked cycle ergometer (Lode Carnival, Lobe BV, Groningen, Netherlands) using indirect calorimetry (Metalyzer 3B, Cortex Biophysik, Leipzig, Germany) with continuous 12-lead ECG monitoring (Custo Diagnostic software, Custo-Med, Ottoburn, Germany). A ramp protocol to volitional fatigue was employed. A maximal test was defined by a respiratory exchange ratio, RER, of >1.1 and a plateau in  $\dot{V}O_2$  over 30-seconds despite increasing workload. The protocol started with a two-minute rest period, then two-minutes of unloaded pedalling, followed by progressive increase in workload based on a workload/min ramp to achieve 8 to 12 minutes of loaded exercise.

Ventilation ( $\dot{V}E$ ), oxygen consumption ( $\dot{V}O_2$ ), expired carbon dioxide ( $\dot{V}CO_2$ ), HR and SpO<sub>2</sub> were monitored continuously, with BP, RPE and perceived SoB recorded every two minutes.

## **Cardiopulmonary imaging/pathology**

### *Cardiothoracic imaging*

High resolution computed tomography (HRCT) and dual-energy CT pulmonary angiography (DECTPA) were performed on a dual-source CT (Siemens SOMATOM Drive, Siemens Healthineers, Erlangen,

Germany), using a HRCT protocol of inspiratory 1mm sections with 10mm gap, and expiratory 1mm sections with a 30mm gap. DECTPA perfusion map and reconstructed 1mm slice thickness were analysed on Siemens Syngo, CT CE Lung Analysis software. Control participants did not undergo CT imaging.

### *Cardiac magnetic resonance imaging (CMR)*

CMRs were acquired on Siemens MR scanners at 3 Tesla (Siemen Medical Solutions, Erlangen, Germany), assessing myocardial mass, volumes and ejection fraction with precordial ECG gating, in held end-expiration. Mapping sequences (ShMOLLI, Siemens) and late gadolinium imaging were obtained with a bolus injection of 0.1mmol/kg of a gadolinium contrast agent. Images were analysed with CVI 42 analysis software (Circle Cardiovascular Imaging Inc, Calgary, AB, Canada).

### **Cognitive Assessment**

Cognitive assessments were performed in a quiet environment using the National Institute of Health (NIH) Cognitive Toolbox cognition battery for age 12+ years on an iPad (Apple, California, USA)(32), with the fluid, crystallised and total composite scores analysed,

### **Patient reported outcome measures**

Participants completed PROMs relating to depression (Patient Health Questionnaire-9, PHQ-9); (33) anxiety (General Anxiety Disorder scale-7 questions, GAD-7); (34) post-traumatic stress disorder (PTSD, National Centre for PTSD checklist, PCL-5);(35) quality of life (QoL, European QoL 5 domains,EQ5D),(36) and fatigue (Fatigue Assessment Scale, FAS).(37) Ongoing symptoms were measured using an evidence-based symptom checklist.(38, 39)

### **Data Management and Statistical Methods**

Study data were collected and managed using REDCap.(40)

### *Statistical Analysis*

Data are presented as mean  $\pm$  standard deviation. The normality of all variables was assessed using a Shapiro-Wilk test and inspection of the frequency histogram distributions and Q-Q plots. Results showed approximate normal distribution across the majority of variables. Parametric tests were applied throughout.

To measure for differences in demographics, functional, neurocognitive and mental health status, and cardiopulmonary function/pathology between the four groups, a one-way analysis of variance (ANOVA) was performed on all continuous data and a chi-squared test on ordinal and categorical data.

An alpha threshold of 0.05 was taken to indicate significance. Post-hoc tests were carried out for any results where a significant between-group difference was identified following an ANOVA. Bonferroni

corrections were applied to allow for multiple post-hoc comparisons.

## RESULTS

At review ( $159 \pm 72$  days following acute illness), hospitalised and community-symptomatic individuals had a mean of  $2 \pm 2$  and  $2 \pm 1$  symptoms (Table 1). Hospitalised individuals were significantly older than both community-symptomatic and community-recovered (Table 2).

**Table 2:** Descriptive data demonstrating body composition, ambulatory function, mental health and fatigue status at admission to DMRC.

	H	CS	CR	CON	F Value	P Value	Post-Hoc Comparison
Number	35	34	18	26			
Age	43 ± 9	37 ± 10	34 ± 6	38 ± 8	4.856	<b>0.003</b>	¶*, †**
<b>Body Composition</b>							
Height (cm)	176 ± 7	179 ± 10	180 ± 8	176 ± 8	1.157	0.330	
Body Mass (kg)	96 ± 15	94 ± 19	83 ± 11	79 ± 8	10.083	<b>&lt;0.001</b>	†*, §***, ¶***
Body Mass Index (kg.m <sup>2</sup> )	31 ± 4	29 ± 4	26 ± 2	25 ± 3	17.909	<b>&lt;0.001</b>	†***, §***, #***, ¶***
Waist Circumference	101 ± 13	96 ± 13	85 ± 10	86 ± 7	13.923	<b>&lt;0.001</b>	†***, §***, #***, ¶**
Waist to Hip Ratio	0.96 ± 0.09	0.94 ± 0.12	0.92 ± 0.09	0.91 ± 0.07	1.272	0.288	
<b>Submaximal Function</b>							
6MWT Distance (m)	603 ± 112	624 ± 82	689 ± 86	719 ± 90	9.357	<b>&lt;0.001</b>	†*, §***, ¶**
<b>Mental Health</b>							
GAD-7 score	4 ± 4	5 ± 5	2 ± 2	2 ± 3	3.899	<b>0.011</b>	
<5 none/minimal, n (%)	18 (51)	21 (62)	17 (94)	23 (88)			
≥10 moderate, n (%)	3 (9)	3 (9)	0 (0)	1 (4)			
≥15 severe, n (%)	1 (3)	2 (6)	0 (0)	0 (0)			
PHQ-9 score	7 ± 5	9 ± 5	3 ± 3	2 ± 3	14.342	<b>&lt;0.001</b>	†*, §***, #***, ¶***
<5 none/minimal, n (%)	12 (34)	6 (18)	13 (72)	24 (92)			
≥10 moderate, n (%)	10 (29)	6 (18)	1 (6)	1 (4)			
≥15 moderate to severe, n (%)	4 (11)	6 (18)	0 (0)	0 (0)			
PCL5 post-trauma stress score	14 ± 14	15 ± 15	5 ± 6	5 ± 8	5.772	<b>&lt;0.001</b>	†*, §*, #*, ¶*
> 32 PTSD cut-off, n (%)	3 (9)	9 (26)	0 (0)	0 (0)			

Quality of Life: EQ5D	66 ± 19	63 ± 22	79 ± 8	79 ± 15	6.066	0.001	§*, #*, ¥**
<b>Fatigue</b>							
FAS	23 ± 8	26 ± 7	17 ± 5	15 ± 4	15.673	<0.001	†*, §***, #***, ¥***
> 21 cut off – fatigued, n (%)	20 (57)	20 (59)	3 (17)	1 (4)			

6MWT, six-minute walk test; GAD-7, general anxiety disorder 7-item checklist, PHQ-9, patient health questionnaire 9 item checklist; PTSD, post-traumatic stress disorder; EQ5D, European Quality of Life 5 domains; FAS, fatigue assessment scale. H, hospitalised illness; CS, community illness with on-going symptoms (community-symptomatic), CR, community illness now recovered (community-recovered; CON age, gender and job-role matched control population. There was no significant difference between CR and CON for any parameter.

†, H vs. CR; §, H vs. CON; #, CS vs. CR; ¥, CS vs. CON; ¶, H vs. CS. Level of significance: \* p<0.05, \*\* p<0.01, \*\*\*p<0.001

## Body composition

Hospitalised and community-symptomatic individuals demonstrate the least favourable body composition (Table 2). There were no significant between-group differences in height or waist-to-hip ratio. However, hospitalised and community-symptomatic individuals both had significantly greater body mass index (BMI) values vs community-recovered and controls (H, 31±4kg.m<sup>2</sup>; CS, 29±4kg.m<sup>2</sup>; CR, 26±2kg.m<sup>2</sup>; CON, 25±3kg.m<sup>2</sup>). Body mass was greater in hospitalised and community-symptomatic individuals, and reviewing waist circumference scores, this can be attributed to increased abdominal fat (H, 101±13cm; CS, 96±13cm; CR, 85±10cm; CON 86±7cm). There was no difference in body composition between community-recovered and controls.

## Blood testing

There were no between-group differences, aside from white cell count between the hospitalised and community-recovered (6.1±1.3×10<sup>9</sup>/L vs 5.0±1.5×10<sup>9</sup>/L) (Online Resource 2).

## Cardiopulmonary Functional Testing

### *Six-minute walk distance*

There was no significant difference in distance walked between community-recovered and control groups (689±86 vs. 719±90m, p>0.05), nor between hospitalised and community-symptomatic groups (603±112m vs. 624±82m, p>0.05) (Table 2). Hospitalised individuals walked 85m less vs community-recovered (p=0.014), and 116m less than controls (p<0.001). Community-symptomatic individuals were not statistically different to community-recovered or controls.

### *Lung function testing*

Post-hoc analyses revealed no significant between-group differences in FEV1, however, FVC values were significantly lower in hospitalised participants vs community-recovered ( $4.7\pm 0.9$  vs  $5.7\pm 0.6$ L,  $p=0.003$ ) (Table 3). One-way ANOVA revealed a significant between-group difference in % predicted DLCO (H,  $83\pm 16\%$ ; CS,  $91\pm 19\%$ ; CR,  $90\pm 14\%$ ; CON,  $98\pm 10\%$ ;  $F=4.132$ ,  $p=0.008$ ). Post-hoc analysis revealed a 15% higher score in % predicted DLCO in controls vs hospitalised ( $p=0.005$ ). No significant between-group differences were reported in % predicted transfer coefficient for carbon monoxide (KCO) (H,  $102\pm 19\%$ ; CS,  $102\pm 12\%$ ; CR,  $96\pm 11\%$ ; CON,  $100\pm 7\%$ ;  $F=0.929$ ,  $p=0.430$ ).

### *Cardiopulmonary Exercise Test (CPET)*

There were no differences between hospitalised and community-symptomatic individuals, or between community-recovered and controls in any CPET variable (Table 3).

### Heart rate profile

Hospitalised and community-recovered individuals had a significantly higher resting HR vs controls ( $82\pm 11$ bpm and  $84\pm 13$ bpm vs  $73\pm 8$ bpm, both  $p<0.05$ ) (Table 3, Figure 2). There were no other between-group differences in exercise HR parameters.

### Oxygen uptake

Hospitalised individuals had lower oxygen uptake ( $\dot{V}O_2$ ) at VT1 [earlier anaerobic transition] vs community-recovered and controls ( $12.3\pm 1.9$  vs  $17.2\pm 3.0$  and  $18.2\pm 5.6$ ml/kg/min, both  $p<0.001$ ). Both the hospitalised and community-recovered groups demonstrate significantly lower values for  $\dot{V}O_2$  at peak exercise vs controls ( $30.5\pm 5.4$  and  $34.4\pm 7.2$  vs  $43.9\pm 13.1$ ml/kg/min, both  $p<0.001$ ) (Table 4, Figure 2). Hospitalised and community-symptomatic groups had a reduced mean predicted  $\dot{V}O_2$  at peak exercise vs community-recovered and controls (Table 3).

Hospitalised participants had lower ventilatory efficiency (higher  $\dot{V}E/\dot{V}CO_2$  slope) than both community-recovered and controls ( $30\pm 5$  vs  $24\pm 6$  and  $26\pm 3$ , both  $p<0.001$ ) (Table 3, Figure 2). There were no other significant between-group ventilatory differences.

### Workload (Watts)

Workloads at VT1 and peak were lower by 36% and 24% respectively in hospitalised individuals compared to controls (both  $p<0.001$ ). Workloads at VT1 and peak were lower by 30% and 25% respectively in hospitalised vs community-recovered ( $p=0.002$  and  $p<0.001$ , respectively). Workloads for VT1 and peak were also less in community-symptomatic vs controls by 22% and 16% ( $p=0.008$  and  $p=0.005$ , respectively) (Table 3, Figure 2). No significant between-group differences were reported in RPE or SoB scores during rest, VT1 or peak exercise, or RER at peak.

**Table 3:** Cardiopulmonary Exercise Testing (CPET) parameters (mean  $\pm$  SD)

Variable	H	CS	CR	CON	F Score	P Value	Post-Hoc Comparison
<b>CPET</b>							
$\dot{V}O_2$ at Rest (ml/kg/min)	4.8 ± 0.9	4.9 ± 1.0	5.5 ± 1.2	5.5 ± 1.8	2.583	0.057	
$\dot{V}O_2$ at VT1 (ml/kg/min)	12.3 ± 1.9	14.5 ± 3.9	17.2 ± 3.0	18.2 ± 5.6	14.665	<0.001	†***, §***, ¥**
$\dot{V}O_2$ at Peak (ml/kg/min)	30.5 ± 5.4	34.4 ± 7.2	44.3 ± 7.4	43.9 ± 13.1	17.788	<0.001	†***, §***, #**, ¥***
$\dot{V}O_2$ at VT1 (% of predicted peak)	41 ± 5	42 ± 6	39 ± 5	42 ± 8	1.141	0.336	
$\dot{V}O_2$ at Peak (% of predicted)	108 ± 16	111 ± 19	122 ± 19	133 ± 25	9.510	<0.001	§***, ¥***
Workload at VT1 (W)	70 ± 15	85 ± 33	100 ± 26	109 ± 34	11.036	<0.001	†**, §***, ¥**
Workload at peak (W)	231 ± 35	255 ± 61	308 ± 60	304 ± 65	12.641	<0.001	†***, §***, #**, ¥**
Workload at peak (% of predicted)	97 ± 17	100 ± 23	115 ± 16	127 ± 32	10.692	<0.001	†*, §***, ¥***
W/Kg at VT1	0.74 ± 0.17	0.92 ± 0.36	1.20 ± 0.29	1.38 ± 0.38	25.266	<0.001	†***, §***, #*, ¥**
W/Kg at Peak	2.44 ± 0.47	2.77 ± 0.68	3.73 ± 0.67	3.89 ± 0.82	14.086	<0.001	†***, §***, #***, ¥***
$\Delta \dot{V}O_2$ (l/min)/ $\Delta$ Work (W)	10.9 ± 1.0	11.2 ± 2.2	11.2 ± 0.9	11.5 ± 0.7	1.971	0.123	
Lactate at rest (mmol/L)	1.3 ± 0.5	1.3 ± 0.5	1.4 ± 0.4	1.2 ± 0.4	0.691	0.559	
Lactate at peak (mmol/L)	12.1 ± 2.5	13.1 ± 2.3	14.1 ± 2.4	14.2 ± 1.5	5.393	0.002	†*, §**
O <sub>2</sub> Pulse	16.7 ± 3.8	18.5 ± 4.7	21.1 ± 3.7	21.1 ± 4.7	7.131	<0.001	†** §**
O <sub>2</sub> Pulse (% of predicted peak)	97 ± 20	105 ± 20	119 ± 17	126 ± 22	12.045	<0.001	†*, §***, ¥*
<b>Heart Rate Profile</b>							
HR at rest (bpm)	82 ± 11	84 ± 13	77 ± 15	73 ± 8	4.791	0.004	§*, ¥**
HR at VT1 (bpm)	106 ±	108 ±	107 ±	107 ±	0.163	0.921	

	14	15	12	8			
HR at peak (bpm)	172 ± 15	175 ± 16	178 ± 7	175 ± 8	0.833	0.479	
% of Predicted max HR	110 ± 10	108 ± 9	107 ± 5	108 ± 7	0.650	0.585	
HRR after 1-min (bpm)	25 ± 10	28 ± 11	30 ± 16	26 ± 8	1.053	0.372	
<b>Blood Pressure (mmHg)</b>							
Resting Systolic BP (mmHg)	126 ± 10	120 ± 11	117 ± 10	121 ± 10	3.670	<b>0.015</b>	†*
Resting Diastolic BP (mmHg)	85 ± 7	84 ± 8	79 ± 8	79 ± 6	5.795	<b>0.001</b>	†*, §**, ¥*
VT1 Systolic BP (mmHg)	142 ± 17	144 ± 15	135 ± 17	142 ± 14	1.381	0.252	
VT1 Diastolic BP (mmHg)	85 ± 17	83 ± 16	76 ± 9	82 ± 12	1.681	0.175	
Peak Systolic BP (mmHg)	169 ± 20	171 ± 18	160 ± 23	166 ± 37	1.392	0.249	
Peak Diastolic BP (mmHg)	73 ± 27	79 ± 19	66 ± 20	73 ± 22	1.526	0.212	
<b>Ventilation</b>							
BF at rest (breaths/min)	17 ± 5	16 ± 5	14 ± 3	16 ± 4	0.998	0.397	
BF at VT1 (breaths/min)	20 ± 7	21 ± 6	18 ± 4	20 ± 4	1.158	0.329	
BF at Peak (breaths/min)	47 ± 12	47 ± 12	46 ± 6	51 ± 11	1.445	0.234	
VE/ V̇CO <sub>2</sub> at Rest	30.8 ± 4.8	30.5 ± 5.3	28.1 ± 2.0	28.0 ± 3.1	3.462	<b>0.019</b>	
VE/ V̇CO <sub>2</sub> at VT1	27.8 ± 4.0	26.7 ± 4.0	24.1 ± 1.7	24.3 ± 2.0	7.807	<b>&lt;0.001</b>	†**, §**, ¥*
VE/ V̇CO <sub>2</sub> at Peak	34.4 ± 5.5	33.2 ± 4.0	30.5 ± 3.1	31.3 ± 3.3	4.431	<b>0.006</b>	†*, §*
VE/ V̇CO <sub>2</sub> Slope	29.6 ± 5.1	27.9 ± 5.3	24.1 ± 6.0	25.5 ± 2.6	6.422	<b>&lt;0.001</b>	†**, §*
pCO <sub>2</sub> Rest	5.2 ± 0.8	4.9 ± 0.6	5.1 ± 0.6	5.1 ± 0.5	1.927	0.130	
pCO <sub>2</sub> Peak	4.5 ±	4.3 ±	4.6 ±	4.4 ±	0.855	0.467	

	0.9	0.8	0.6	0.6			
OUES	3.01 ± 0.58	3.34 ± 0.96	4.88 ± 1.11	3.79 ± 0.93	3.689	<b>0.014</b>	†**
<b>Resting Spirometry</b>							
FEV1 value (L)	3.7 ± 0.6	3.9 ± 0.8	4.3 ± 0.4	4.1 ± 0.6	2.859	<b>0.041</b>	
FEV1 % predicted	96 ± 14	93 ± 11	97 ± 14	102 ± 13	2.362	0.076	
FVC value (L)	4.7 ± 0.9	5.2 ± 1.1	5.7 ± 0.6	5.3 ± 0.7	4.751	<b>0.004</b>	†**
FVC % predicted	99 ± 14	101 ± 13	106 ± 11	108 ± 10	3.142	<b>0.028</b>	§*

Abbreviations: VT1, 1<sup>st</sup> ventilatory threshold; HR, heart rate; HRR, heart rate recovery; BP, blood pressure; BF, breathing frequency; OUES, oxygen uptake efficiency slope. H, hospitalised illness; CS, community illness with on-going symptoms (community-symptomatic), CR, community illness now recovered (community-recovered; CON age, gender and job-role matched control population. There was no significant difference between H versus CS and CR versus CON for any CPET-related parameter.

†, H vs. CR; §, H vs. CON; #, CS vs. CR; ¥, CS vs. CON. Level of significance: \* p<0.05, \*\* p<0.01 \*\*\*p<0.001

### *Cardiopulmonary imaging*

Imaging results were reviewed by consultants in radiology, cardiology and respiratory medicine to determine clinical significance (Table 4). The only clinically significant pathology identified, moderate volume ground glass changes, occurred on two HRCTs.

**Table 4:** Prevalence of participants with abnormal and clinically significant findings following clinical investigations. Descriptive data detailing the total number in each group and percentage based on the number of tests performed.

	H	CS	CR	CON
<b>CT</b>				
Tests Performed	34	34	18	0
Abnormal Result	20 (58%)	2 (6%)	2 (11%)	--
Clinically Significant	2 (6%)	0 (0%)	0 (0%)	--
<b>CTPA</b>				
Tests Performed	32	34	18	0
Abnormal Result	8 (25%)	1 (3%)	0 (0%)	--
Clinically Significant	0 (0%)	0 (0%)	0 (0%)	--
<b>CMR</b>				
Tests Performed	35	34	18	26
Abnormal Result	4 (11%)	5 (15%)	3 (17%)	1 (4%)
Clinically Significant	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Abbreviations: CT, computerised tomography; CTPA, computerised tomography pulmonary angiogram; CMR, cardiovascular magnetic resonance imaging. H, hospitalised illness; CS, community illness with on-going symptoms (community-symptomatic), CR, community illness now recovered (community-recovered); CON age, gender and job-role matched control population.

### Cognitive function

There were no between-group differences in fluid, crystallised or total composite scores (Supplementary File 2).

### Mental health and quality of life

The mean scores for anxiety and depression equated to 'minimal' (0 to 4) or 'mild' (4 to 9) severity for each group (Table 2). Post-hoc analyses revealed no significant between-group differences for anxiety. However, there were significant differences for depression between hospitalised and community-recovered ( $p=0.042$ ), hospitalised and control ( $p<0.001$ ), community-symptomatic and community-recovered ( $p=0.001$ ) and community-symptomatic and control ( $p<0.001$ ) (H,  $7\pm5$ ; CS,  $9\pm5$ ; CR,  $3\pm3$ ; CON,  $2\pm3$ ). The number of hospitalised and community-symptomatic participants scoring 'none or minimal' or ' $\geq$ moderate symptoms' differed vs community-recovered and controls (Table 2). Only half of hospitalised individuals reported 'none or minimal' anxiety, and one third 'none or minimal' depression, vs  $\sim 90\%$  of controls. 29% and 18% of hospitalised and community-symptomatic individuals reported ' $\geq$ moderate depression' vs 4% of controls. PTSD scores were higher in the hospitalised and community-symptomatic

vs community-recovered and controls ( $p < 0.05$ ). Hospitalised and community-symptomatic participants had lower QoL vs controls ( $p < 0.05$ ), and community-symptomatic vs community-recovered ( $p < 0.05$ ).

## Fatigue

Mean FAS values were significantly higher for hospitalised individuals vs community-recovered ( $23 \pm 8$  vs.  $17 \pm 5$ ,  $p = 0.017$ ) and controls ( $15 \pm 4$ ,  $p < 0.001$ ) (Table 2). Mean FAS values were also significantly higher in the community-symptomatic ( $26 \pm 7$ ) vs community-recovered and controls (both  $p < 0.001$ ).

## DISCUSSION

In a physically active working-age population, this study found that individuals who had recovered following community-based acute illness did not differ from an age, gender and job-role matched control population across a comprehensive array of cardiopulmonary, functional, neurocognitive and mental health assessments.

### Participant characteristics/demographics

There were no between-group differences in highest educational attainment or rank, as proxies for socio-economic status (Supplementary file 2), but significant between-group differences were demonstrated in age and body composition ( $p > 0.05$ ). Both hospitalised and community-symptomatic individuals were significantly older, had increased body mass, BMI and waist circumference vs community-recovered, consistent with increased age and BMI as risk factors for COVID-19 severity.(7, 41, 42)

### Functional limitations

Hospitalised and community-symptomatic participants had reduced exercise capacity during sub-maximal (6MWT) and maximal testing (CPET). They also achieved significantly shorter 6MWT distances vs controls, with higher pre- and post-6MWT breathlessness scores. No significant differences in distance were observed between community-recovered and control groups. Other studies (21, 43) have found similar discrepancies in 6MWT, albeit at much shorter distances, reflecting the pre-morbid fitness of participants in this study.

During CPET, hospitalised and community-symptomatic participants had lower absolute and relative  $\dot{V}O_2$ , and workload at both VT1 and peak, with significantly lower peak lactate and  $O_2$  pulse values. Hospitalised individuals also had higher  $\dot{V}E/\dot{V}CO_2$  slopes, and therefore worse ventilatory efficiency compared to the other three groups. Lower  $\dot{V}O_2$  and higher  $\dot{V}E/\dot{V}CO_2$  slopes have previously been reported in individuals with more severe COVID-19 illness.(21, 25, 26)

There were no significant differences demonstrated between the community-recovered and controls in  $\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  values. Whilst Singh *et al.*(20) reported reduced  $\dot{V}O_2$  max with increased  $\dot{V}E/\dot{V}CO_2$

slopes during CPET in their 'recovered individuals', (20) their study participants were recruited from an unexplained exercise intolerance clinic, failing to meet our definition of 'recovered'.

## **Organ pathology**

Despite concerns regarding end-organ damage after COVID-19, (3, 22, 23, 41, 44-46) especially in athletes, (47) this study reassuringly demonstrates an extremely low level of abnormalities in cardiopulmonary imaging, blood markers or cognitive function across the spectrum of severity. Hospitalised individuals were more likely to have pathological findings on imaging, however, only 6% were deemed clinically significant, a much lower rate than the 29-60% previously reported (within methodological differences) (Table 2) (21, 43, 48). This could be due to the protective effect of cardiorespiratory fitness and lean muscle tissue/metabolic flexibility in this trained population. (49, 50) Importantly, there were no differences on any endpoint measured between the community-recovered and control groups.

Neurocognitively, the fluid composite score, the ability to react, analyse and process information, and the crystallised composite score, representing acquired knowledge and learning, were reviewed. The former is impacted by biological insult, while the latter is relatively preserved. Our findings suggest no medium-term damage, with no statistically significant differences between composite cognitive scores in this study. Previous work have shown cognitive symptoms improving with time. (51, 52)

Lung function results were also reassuring in this study. The only demonstrable effects were an 18% reduction in FVC in hospitalised vs. community-recovered, and a 15% reduction in DLCO for hospitalised vs. controls. The coincidence of relatively reduced FVC and DLCO in those hospitalised, with no difference in KCO, is suggestive that these differences result from a reduced lung volume, rather than a problem of ventilation-perfusion matching. Previous studies have highlighted the need to correlate both spirometry and diffusion capacity (21, 46).

## **Mental health**

There were between-group differences in mental health status, fatigue and QoL. The impact of the virus can be partitioned, by using a control group, to separate out the impact of social upheaval, isolation, media and other external influences. (53, 54) Those in the community-symptomatic group had the highest scores for anxiety, depression and fatigue and the lowest for QoL. Those in the hospitalised group scored highest for post-traumatic stress. There were no significant differences between hospitalised and community-symptomatic groups, similarly to other study populations, (42) and the 2003/4 SARS epidemic. (55, 56) Community-recovered participants displayed no significant difference to controls.

## **Strengths and limitations**

This is the first study, to our knowledge, that has compared groups, across the spectrum of acute COVID-19 severity, including on-going or resolved symptom cohorts, with an age, gender and job-role matched control group, to identify ongoing organ pathology, functional limitations and mental health impact.

Whilst the sample size (n=113) is modest, this is balanced by the comprehensive assessment completed in every participant.

Non-recovery was defined by the presence of symptoms at the time of recruitment (~5 months post illness). The most common symptoms (Table 1) are reflective of those in other studies, which supports the generalisability of other findings here, such as objective cardiopulmonary fitness and neurocognitive outcomes, which have not previously been reported in case-controlled cohorts.(42, 57-59)

An additional strength is the population studied. Whilst not all findings can be extrapolated to the wider population, the impact on COVID-19 on sportspeople and other physically demanding occupations has been a research priority.(60) The findings of this study will reassure the majority of recovered individuals with less severe disease, and the clinicians responsible for their care. It will permit the dedication of resources to those who remain at risk of important clinical sequelae. All investigations were delivered by the same team of investigators, equipment and conditions, increasing the consistency of the data.

## CONCLUSION

This study showed that those with more severe acute disease and/or prolonged symptoms were older and had a higher BMI. Within these groups, there is an increased likelihood of pathological cardiopulmonary imaging findings (albeit at a much lower rate than other published studies) and reduced exercise capacity during sub-maximal and maximal testing. These same groups also experienced higher rates of mental health symptoms, fatigue, and a reduced QoL.

Reassuringly, this study also found that recovered community-based individuals do not differ in terms of cardiopulmonary disease, functional outcomes and mental health from a matched control population. Our findings do suggest that for individuals who will be exposed to high intensity physical exercise, who were either hospitalised during acute illness or experience prolonged symptoms, that a specific, comprehensive evaluation of functional and neurocognitive capacity, mental health status and cardiopulmonary pathology is warranted.

## Declarations

**Ethical approval and consent to participate:** Ethical approval from the Ministry of Defence research ethic committee in July 2020 (1061/MODREC/20).Written informed consent was obtained from all participants included in the study.

**Consent for publication:** Written informed consent included consent for anonymised data to be analysed and shared (including via publication).

**Data sharing:** Data relate to the serving population of the Ministry of Defence and thus are sensitive. Research teams requesting data are invited to contact the corresponding author and appropriate permissions will be sought for release.

**Conflict of interest:** No authors have any conflicts of interest to declare.

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**Contributorship statement:** DH, EN, OOS, RBD, JMi, PL and ANB conceived the study. DH, EN and ANB secured funding and established additional clinical investigations to deliver the research. DH, RC, ES, CX, NT and KP coordinated the delivery of investigations in Oxford. RBD, OOS, PL, RC, DD, SM, DM, JMu and DH acquired data at DMRC. RC, KP, CX, ES, OR acquired data in Oxford. DH, EN, JMu, JN, MC, OR, CX and ES provided clinical opinion/reporting. AH provided statistical analysis. OOS, with support from DH, PL and ANB drafted the manuscript. All authors reviewed the manuscript.

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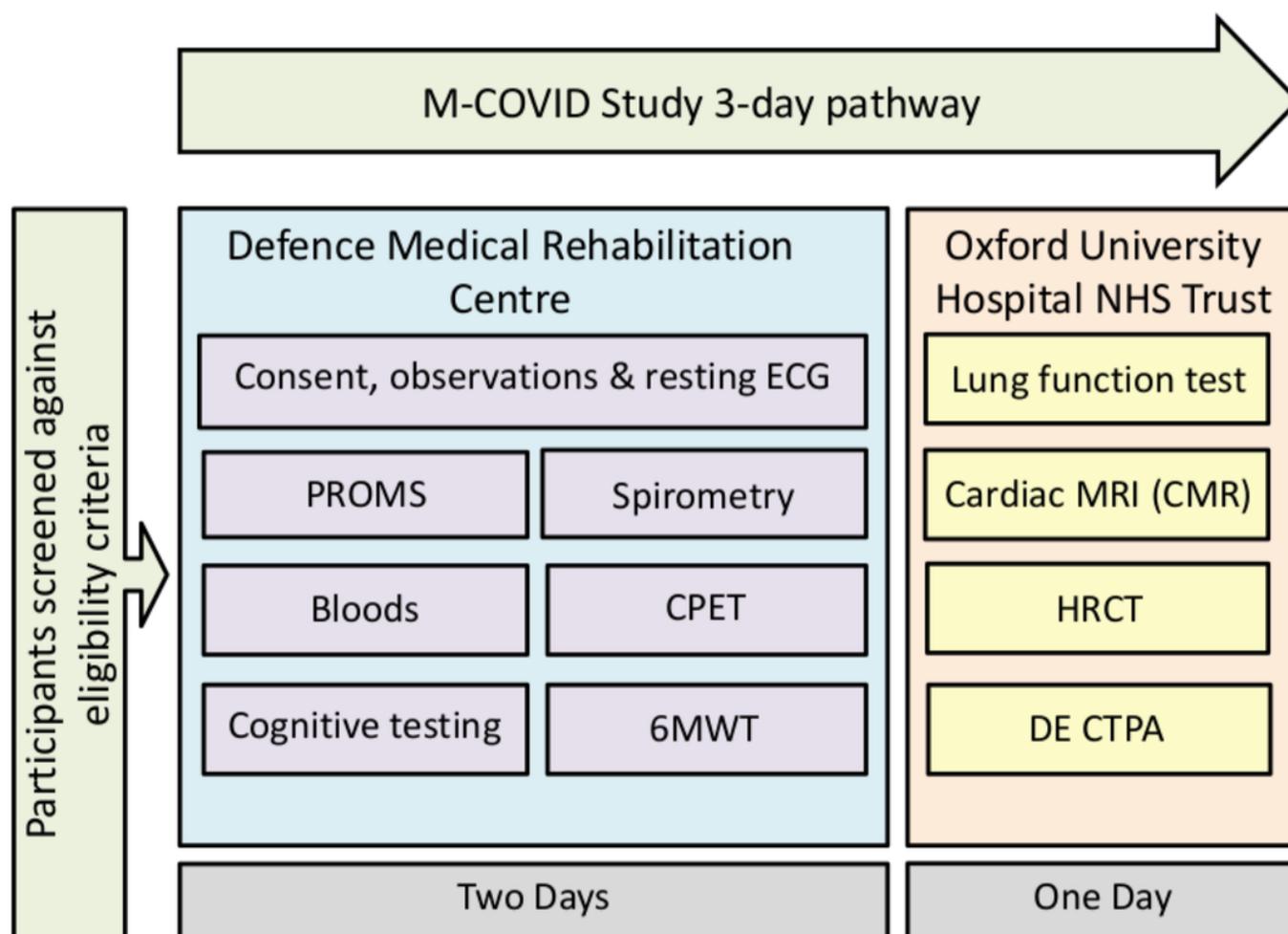
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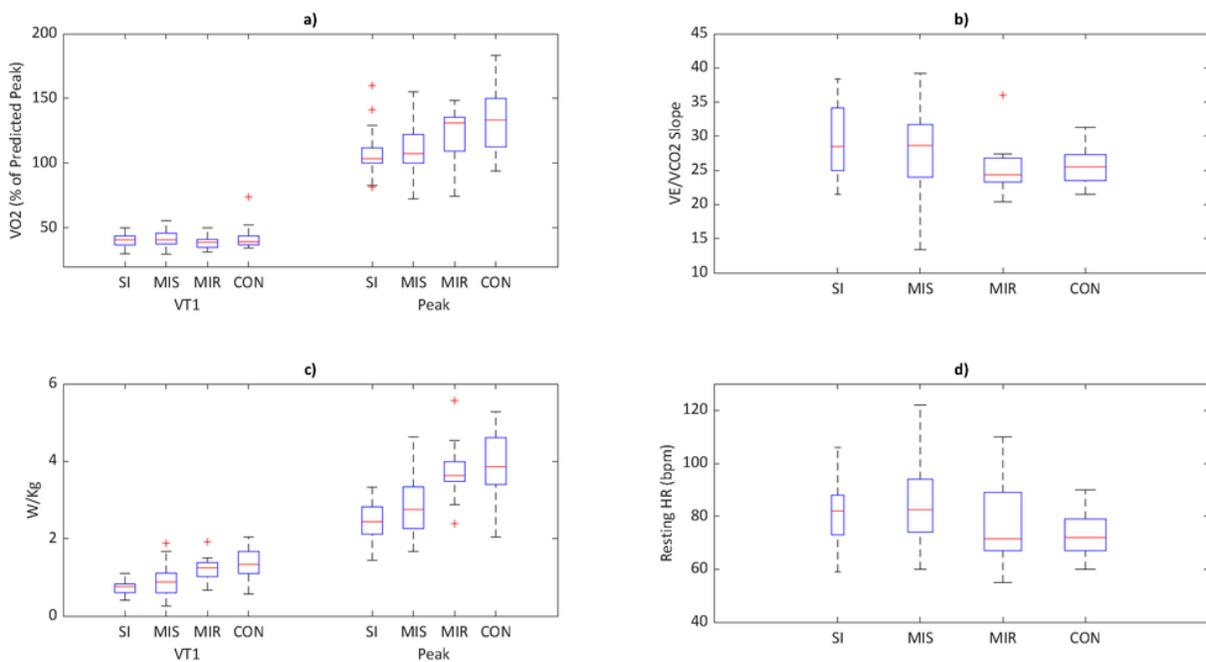
## Figures



## Figure 1

Diagrammatic description of study design.

Abbreviations: ECG, electrocardiogram; PROMS, patient reported outcome measure; CPET, cardiopulmonary exercise test; 6MWT, six-minute walk test; MRI, magnetic resonance imaging ; CMR, cardiac magnetic resonance imaging; HRCT, high-resolution computed tomography; DE CTPA, dual-energy computed tomography pulmonary angiogram.



## Figure 2

Cardiopulmonary exercise test (CPET) variables: a) percentage predicted VO<sub>2</sub> at VT1 and peak, b)  $\dot{V}E/\dot{V}CO_2$  slope, c) workload (watts per kilogram) at VT1 and peak, d) resting heart rate.

## Supplementary Files

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