**Title:** Profiling the persistent and episodic nature of Long COVID symptoms and the impact on quality of life and functional status: A Cohort Observation.

**Authors:**

Rebecca Owen 1, Ruth EM Ashton 2, Tom Bewick 3, Robert J Copeland 4, Francesco V Ferraro 1, Clare Kennerley 4, Bethan E Phillips 5, Thomas Maden-Wilkinson 4, Thomas Parkington 4, Lindsay Skipper 1,6, Callum Thomas 1,Mark A Faghy1.

**Author Affiliations:**

1. Biomedical and Clinical Science Research Theme, School of Human Sciences, University of Derby, Derby, UK
2. Research Centre for Physical Activity, Sport and Exercise Sciences (PASES), Institute of Health and Wellbeing (IHW), Coventry University. Coventry, United Kingdom.
3. Department of Respiratory Medicine, University Hospitals of Derby and Burton NHS Foundation Trust, Uttoxeter Road, Derby, DE22 3NE, UK.
4. Physical Activity, Wellness and Public Health Research Group, School of Sport and Physical Activity, Sheffield Hallam University, Sheffield, UK
5. School of Medicine, University of Nottingham, Nottingham and Derby, UK
6. Patient and Public Involvement and Engagement Representative, Derby. UK.

**Correspondence to:** Ms Rebecca Owen, Lecturer in Sport and Exercise Physiology, Biomedical and Clinical Exercise Research Theme, University of Derby, Derby, UK. R.owen@derby.ac.uk 01332 592109.

**Summary**

Background: Post-viral issues following acute infection with COVID-19, referred to widely as Long COVID are associated with episodic, persistent, and disabling symptoms affecting quality of life and functional status. Evidence demonstrates a significant impairment and long disease course but there remains limited empirical data to profile and determine the fluctuating symptom profile of Long COVID.

Methods: Accordingly, we devised a 16-week, multicentre prospective cohort observation to profile changes in patient-reported outcomes, biological, physiological, psychological, and cognitive parameters following diagnosis and/or referral to an established Long COVID clinic. Following baseline assessments, participants completed four face-to-face visits interspersed with telephone consultations. Face-to-face visits included physiological assessment, patient-reported outcome measures (PROMs), functional status, and respiratory function. Telephone consultations involved PROMs and symptom profiling.

Results: Patient-reported outcomes improved from baseline to week sixteen but demonstrated between visit fluctuations in frequency and severity.Findings highlight the severity and frequency of Long COVID symptom profiles and the extent of quality of life and functional status impairment.

Conclusions: Data presented here highlights the episodic and relapsing nature and should be used to help characterise Long COVID disability and inform the development of Long COVID-specific guidelines and support services that can adequately respond to the reductions in patient wellbeing.

**Funding**: This study was supported by an unrestricted investigator-sponsored research grant from Gilead Sciences (#IN-UK-983-6080).

**Keywords:** COVID-19, Long COVID, quality of life, functional status, chronic disease.

**Introduction**

Symptoms of acute viral infections that persist in the weeks, months and years post-infection are collectively referred to as post-viral illnesses. The most devastating epidemic in recorded history is the 1918 Spanish Flu epidemic which has an estimated global mortality between 24-50 million people, over three distinct waves of infection (1). Of particular interest was the high prevalence of reported complications and impaired recovery, with physical exertion and fatigue being documented as important limiting factors. More recent epidemics, including SARS-CoV or SARS-CoV-1 (2002-2004) have also demonstrated persistent symptoms that impact functional status and quality of life with evidence showing sustained impact at 12 months post-infection (2). This narrative is consistent with the SARS-CoV-2 (COVID-19) virus that arose in 2019 and resulted in global transmission leading to a total reported cases of >771 million and >6 million deaths. The actual figures are likely to be much higher due to the time required to develop and provide access to testing, which has subsequently been removed as part of the world's approach to living with COVID-19. Furthermore, viral proliferation due to COVID-19’s use of ribonucleic acid (RNA), its transmission via airborne particles (3), coupled with the removal of all mitigation strategies, has resulted in highly mutated variants being circulated globally and remain a threat to global health and wellbeing (4). SARS-CoV-2 is known to evolve at an approximate rate of 1.1×10− 3 substitutions per site per year, equivalent to a single substitution every 11 days (5). Whilst recognised that not all mutations pose a threat to public health, previous variants including Omicron (B.1.1.529, BA.1, BA.1.1, BA.2 ((including BA.2.86)), BA.3, BA.4 and BA.5 lineages) and Delta (B.1.617.2 and AY lineages) are widely regarded as variants of concern (6), due to several mutations affecting the spike protein, thus increasing transmissibility (7).

Post-viral complications following an acute infection with COVID-19, referred to as post-acute COVID syndrome or more widely as Long COVID, is associated with persistent, and often disabling symptoms that affect quality of life and functional status (8). Consistency in clinical definitions, and implementation of appropriate reporting methods together with a dearth of pathophysiological and mechanistic understanding make it difficult to provide accurate estimations of those living with Long COVID. It is suggested that one in ten people experience persistent symptoms that are not resolved at 12 months following a COVID-19 infection, and global trends estimate that it affects 65-150 million people worldwide (9, 10). In response to the emerging narrative of persistent and debilitating symptoms in Long COVID, a series of studies were established to quantify patient outcomes and pathophysiologic function over time. Cohort observation study designs are commonplace in clinical research settings to identify and evaluate causes, risks or changes in diseases or health-related events. Within their very nature, cohort observations can take a prospective or retrospective approach. Retrospective cohort designs have been widely implemented and make use of existing data sets that are recorded in clinical settings to determine the long-term outcomes for patients in specific clinical areas. In the context of Long COVID, Taquet *et al*, (2021), conducted a retrospective cohort study via electronic health records data from >81 million patients including 273,618 COVID-19 survivors (11). The data revealed that 57% had at least one feature of Long COVID during the 6-month study period, which was not resolved at 12 months in 37% of cases. The most reported symptoms included abnormal breathing (18%), fatigue/post-exertional malaise (13%), chest/throat pain (13%;), headache (9%), other pain (12%), abdominal symptoms (16%), myalgia (3%), cognitive symptoms (7%), and anxiety/depression (23%). Whilst it is recognised that these approaches allow fast analysis of large data sets and conclusions to be derived quickly, these approaches are limited and cannot be used to establish definitive causality in chronic disease. Additionally, retrospective approaches are not designed to support closer inspection and determination of regular fluctuations in symptom profiles and the ongoing persistence of clinical features that affect everyday life.

The use of prospective cohort observations has also produced data that has been intentionally designed and used to increase knowledge of risk factors and patient outcomes over a period following an infection with COVID-19. Most notably in the United Kingdom, the Post-hospitalisation COVID-19 study (PHOSP) was established to increase the understanding of why some recover more quickly than others, why patients develop other health problems and to determine which treatments received in hospital or afterwards that were helpful, collectively seeking to improve the care of patients after they have been discharged from hospital. In a tiered approach, PHOSP recruited ~10,000 patients over two years and has reported widespread sequelae across a range of health domains in hospitalised COVID-19 patients that remained substantial 12 months after discharge with only a minority reporting feeling fully recovered (12). Further exploration within this consortia has also reported widespread physical, cognitive, and mental health impacts, models of predicting reduced patient outcomes using bio-marker analysis (13) and extensive multiorgan abnormalities (14). The nature and design of prospective studies permit insight over prolonged periods from a clinical perspective, and data can be collected and analysed about important health and wellbeing outcomes about prognosis and to evaluate the efficacy of interventions. Evidence to date demonstrates significant impairment and a long disease course (>12 months) but there remains little insight into the episodic and debilitating nature of Long COVID which is prone to exacerbation. Accordingly, this study set out to profile with frequency and by using mixed methods approaches, changes in the patient-reported outcomes, biological, physiological, psychological, and cognitive parameters in the 16 weeks following a confirmed diagnosis and/or referral to an established Long COVID clinic.

### **Method**

Following institutional and NHS ethical approval (IRAS ID: 292920), a 16-week prospective observation cohort study took place at the University of Derby and Sheffield Hallam University. Data collection started in June 2020 and finished in May 2023.

#### *Recruitment, screening, and eligibility*

Hospitalised patients were assessed according to the eligibility criteria and recruited directly from Derbyshire Community Health Services and Sheffield Teaching Hospitals NHS Foundation Trust. Long COVID patients were also assessed according to the eligibility criteria and were recruited following referral/contact with a Long COVID clinic or having suspected or confirmed Long COVID. Social media and targeted recruitment from established pages were used to advertise the opportunity to engage with the trial. Inclusion criteria included participants scoring two or more on the post-COVID-19 Functional Status Scale (PCFS), being admitted to hospital for treatment of COVID-19 or persistent symptoms consistent with Long COVID, being over 18 years and able to understand verbal or written information in English. Those who did not meet this inclusion criteria, and/or had reduced or lack of mental capacity were excluded.

#### *Experimental Protocol*

The determinants of recovery were profiled using a mixed-method approach. Participants attended a total of 5 face-to-face visits each occurring ~4 weeks, interspersed by bi-weekly telephone calls, shown in Figure 1. On each face-to-face visit, physiological variables, patient-reported outcome measures (PROMs), functional status tests (6-Minute Walk Test, Timed Up and Go), and respiratory function tests were complete. During telephone consultations, PROMs and symptom profiling were completed, and details of contact with healthcare services were taken.

****

Figure 1: Experimental Protocol

#### *Baseline visit*

Following screening, anthropometric data, including height and weight, date of birth, sex, past medical history, smoking history, and occupational status were collected. Details regarding admission and contact with primary and secondary care was taken for those who had been hospitalised due to either acute or Long COVID related symptoms. A venous blood sample was taken from the antecubital fossa region of the arm measuring inflammatory and metabolic markers (Full blood count [FBC], red blood cells [RBC], white blood cells [WBC], Haemoglobin, Haematocrit, Mean Corpuscular Volume [MCV], Mean Corpscular Haemoglobin [MCH], Mean Corpuscular Haemoglobin Concentration [MCHC], Red Cell Distribution Width [RDW], Platelets, Neutrophils, Lymphocytes, Eosinophils, Monocytes, Basophils], Ferritin, D-Dimer, C-Reactive Protein; [CRP], Lactate dehydrogenase [LDH],).

#### **Patient-reported outcome measures (PROMs):**

##### *Post-COVID-19 Functional Status Scale (PCFS)*

The PCFS was developed to assess recovery following COVID-19 infection covering the entire range of functional limitations, such as changes in lifestyle and social activities (15). The PCFS determines how much an individual is affected in their everyday life by COVID-19, from having no limitations (0) to suffering from severe limitations in everyday life, without being able to care for themselves and being dependent on nursing care and/or assistance from another person due to symptoms, pain, depression, and anxiety (4).

##### *EQ-5D-5L*

The EQ-5D-5L is a commonly used assessment for quality of life comprising five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression(16). Each dimension has five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. A visual analogue scale is used to record the patient’s self-rated health, with endpoints ‘the best health you can imagine’ and ‘the worst health you can imagine.’

##### *Medical Research Council (MRC) Dyspnoea Scale*

The MRC Dyspnoea Scale is a valid method used to assess the degree to which dyspnoea affects functional ability on a scale of 0-4(17). The scale measures perceived respiratory disability, allowing patients to indicate the extent of breathlessness on their mobility.

##### *Fatigue Assessment Scale (FAS)*

The FAS is a 10-item self-report scale evaluating symptoms of fatigue. The FAS treats fatigue as a unidimensional construct, measuring both physical and mental symptoms(18). The total score ranges from 10-50, with a higher score accounting for more severe fatigue. A total score of <22 indicates a healthy level of fatigue, 22-34 mild-to-moderate fatigue, and 35+ severe fatigue.

##### *Modified Fatigue Impact Scale (MFIS)*

The MFIS is a 20-item self-reported questionnaire assessing fatigue, consisting of nine ‘physical’, ten ‘cognitive’ and two ‘psychosocial’ items(19). Higher scores indicate a greater impact of fatigue on quality of life and are calculated for each subscale (physical; 0-36, cognitive; 0-40, psychosocial; 0-8) with a maximum total score of 84(19).

##### *Montreal Cognitive Assessment (MoCA)*

The MoCA is a widely used assessment in clinical settings and research. It is a validated, highly sensitive measure used for early detection of mild cognitive impairment, assessing short-term memory, visuospatial abilities, executive functions, attention concentration and working memory, language and orientation of time and place(20). Two distinct versions of the MoCA were used as recommended to reduce the impact of the learning effect.

##### *Symptom profile:*

Patients reported and described symptoms and the impact these have on daily life on a scale of 0-10. The symptom score measure was also completed, detailing the severity of symptoms for the previous 24 hours.

#### **Functional Status:**

Functional tests were completed on each face-to-face visit.

##### *6-minute Walk Test (6MWT)*

The 6MWT is a standardised and widely used measure of functional status as well as assessing responses to interventions and predicting morbidity and mortality(21-23). The 6MWT was conducted according to published guidelines from the 2002 American Thoracic Society (24). The participant was instructed to walk up and down the corridor, covering the greatest distance possible over 6 minutes.

##### *Timed Up and Go (TUG)*

The TUG is a reliable measure accepted for use across multiple clinical populations and is validated as a predictor of frailty and risk of falls in elderly adults(25). Participants were instructed to stand from a seated chair with armrests and walk to and from a three-meter marker where they were required to tap the practitioner’s hand and sit back down(26). A total of three attempts were timed, with the quickest recorded as the best effort.

#### **Physiological Measures:**

Physiological variables were measured on each face-to-face visit.

Blood oxygen saturation was measured using a Nonin Medical Pulse Oximeter (Model 2500, Nonim Medical, INC., Plymouth, MN, USA). Resting heart rate and blood pressure were measured using an automatic blood pressure monitor (Omron M2, Omron Healthcare Co Ltd., Kyoto Japan). Core body temperature was recorded via a tympanic reading using a Braun thermometer (Braun Thermoscan model 6022, Germany).

##### *Lung and Respiratory Muscle Function*

Maximum Inspiratory Pressure (MIP) and Maximum Expiratory Pressure (MEP) measurements were taken on face-to-face visits, according to published guidelines(27). MIP was assessed using a hand-held respiratory pressure meter (RP Check, MD Diagnostics Ltd., Maidstone, UK) with an occluded nasal pathway. Manoeuvres were initiated from residual volume and a maximal inspiratory effort was maintained for 3 seconds. Similarly, MEP was assessed using the same hand-held device, however, participants initiated the manoeuvre from total lung capacity followed by a maximal expiration maintained for 3 seconds. The best of three consecutive values within either 10% or, if lower, 10cmH20 was taken as the values for MIP and MEP. However, if this condition was not met, the average of the three highest values from ten efforts was taken as the values(27).

A hand-held, electronic spirometer (SpiroConnect, MedChip Solutions Ltd., Kent, UK) was used to measure Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV1), FEV1: FVC ratio, and Peak Expiratory Flow (PEF) with an occluded nasal pathway while seated. Manoeuvres were taken by appropriate guidelines (28) and were initiated from total lung capacity. A maximal expiratory effort was maintained for 5 seconds; a minimum of three attempts were performed with an acceptability criterion being when there was a ≤0.150 L differences between the largest and next largest FVC and FEV1 measurements (29). Breathing rate was assessed while seated at rest by observing participants' chest rise and fall over a 10-second period, which was then extrapolated to provide a one-minute breathing rate.

#### *Data analysis*

Raw data from the CRF was transferred to Excel. Python and SPSS (Version, 29.0.1.1) were used for the analysis of descriptive statistics (mean±, median, interquartile range), box plots, sphericity, and one-way ANOVA with repeated measures (RMA). Due to its robustness, where the assumption of normality was not met, but sphericity was assumed, an RMA was used(30). In line with the literature and where 5-10% of data were missing (31) multiple imputation (MI) was used. The MI model in SPSS was used to replicate the incomplete dataset five times and replace the missing data in each replicate with plausible values. Single MI was calculated by combining the estimates obtained from each completed dataset and pooling the data according to Rubin’s Rules(32, 33). MI was used for missing data for those who did not reach the end of the study but had completed >2 face-to-face visits [n=8](31, 34). Where worsening symptomology resulted in a participant being unable to perform a measure, MI was not used. Normative data and expected values were used for comparison to this cohort.

**Results**

Characteristics for seventy-five participants including vaccination status, comorbidities and duration since infection are presented in Table 1. The mean time from infection to date of participation was 1 year and 2 months. Seven participants were hospitalised during acute COVID-19 infection, with length of stay ranging from 1-32 days. At the time of the baseline visit, 99% were vaccinated with 54.7% receiving three doses. One or more comorbidities were experienced by 89% of participants, and 73.3% of participants were non-smokers.

Table 1: Participant characteristics

|  |  |  |  |
| --- | --- | --- | --- |
| **Demographics****(%)** | **Time since infection** | **Vaccination Status****(%)** | **Comorbidities (%)** |
| Females: 65Age: 48 ± 12 yearsNon-smoker: 73.3Previous smoker: 28.8Smoker: 1.3 | Mean: 1 year 2 monthsMedian: 425 daysMin: 14 daysMax: 1158 days | Vaccinated: 991 dose: 72 doses: 303 doses: 554 doses: 8Pre-LC: 53Post-LC: 35 | Endocrine: 15Renal: 8Cardiovascular: 28Gastrointestinal: 45Neurological/Cerebrovascular: 28Malignancy (including haematological): 11.Other: 77None: 111 comorbidity: 192 comorbidities: 293+ comorbidity: 36 |

*Long COVID Symptoms*

Cumulative symptom score relative to severity was 28 ± 14 AU at baseline and post-hoc analysis determined statistically significant differences between week 6 (29 ± 14 AU) and week 16 (25 ± 14 AU, *p<.007*), and week 14 (30 ± 16 AU) and week 16 (*p=<.001*), shown in Figure 2. Fatigue was the most reported symptom across the 16 weeks, followed by difficulty concentrating. The prevalence of other symptoms varied over the 16 weeks but consisted of headaches, difficulty sleeping and cognitive disturbance (figure 3).



Figure 2: Symptom Score over 16-weeks with P Values.



Figure 3: Symptom reporting heat map showing number of participants reporting the symptom over 16 weeks.

*Patient Reported Outcomes*

Cognitive function improved from baseline (23 ± 9 AU) to week 4 (27 ± 2 AU, *p=.038);* week 8 (27 ± 2 AU, *p=<.001),* week 12 (28 ±2, *p=<.001),* and week 16 (28 ± 2 AU, *p=<.001).* There were further improvements between week 4 and week 12 (*p=.040)* and week 16 (*p=.010)* (Figure 4).Dyspnoea was 3 ± 1 AU at baseline and was unchanged at any time point. FAS indicates severe fatigue at baseline (34 ± 9 AU), with an improvement whereby each week the FAS score was reduced to mild-moderate fatigue with a global significance of *p=*.034 (Figure 4). This trend fluctuated between time points, with a final score of 31 ± 10 AU. Fatigue was further assessed with the MFIS and the cumulative score at baseline (59 ± 15 AU) followed a similar trend to FAS, with levels of fatigue fluctuating across the 16-weeks. There was a significant change from baseline to week 2 (54 ± 17 AU, *p=.032)*, week 4 (53 ± 16 AU, *p=*<.001), week 6 (53 ± 19 AU, *p=*.010), week 8 (51 ± 18 AU *p=*<.001), week 10 (52 ± 19 *p-<.001),* week 12 (50 ± 19 AU *p=<.001)* week 14 (51 ±20 AU *p=*<.001) andweek 16 (49 ± 21 AU, *p*=<.001*).*When analysed for each subsection (Figure 5) of the MFIS, physical fatigue had a significant improvement from baseline (28 ±5 AU) to week 2 (25 ± 7 AU, *p=*.041);week 4 (25 ± 7, *p=*.002) week 6 (25 ± 8 AU, *p=*.008), week 8 (24 ± 8, *p=*.001), week 10 (25 ± 8 AU *p=.023),* week 12 (24 ± 8 AU *p=*.002)week 14 (24 ± 8 AU, *p=*.005) and week 16 (23 ± 9 AU *p=*.<.001). Cognitive fatigue was 26 ± 9 AU at baseline and followed a similar trend of improvement from baseline to week 8 (22 ± 10, *p=*.005), week 10 (22 ± 10, *p=.*012*),* week 14 (22 AU ± 11 *p=.*012*)* and week 16 (22 ± 11, *p=.*001*).* Psychosocial fatigue followed a similar trend, improving from baseline to week 4 (5 ± 2 AU, *p=*.002), week 8 (5 ± 1 AU, *p=*.001), week 12 (5 ± 2 AU, *p=.013)* and week 16 (5 ± 2 AU *p*=<.001*)* (Figure 5)*.*



Figure 4: Fatigue Assessment Scale, Dyspnoea Scale and Montreal Cognitive Assessment (MoCA) over 16 weeks with P Values.



Figure 5: Modified Fatigue Impact Scale (Total, Physical, Cognitive and Psychosocial) over 16 weeks with P Values.

*Quality of Life*

Across the 16 weeks, the mean utility index score for the EQ-5D-5L ranged from 0.002-1 but did not significantly change between time points (figure 6). The mean EQ visual analogue scale improved between week 6 (50 + 20 AU) and week 16 (57 ± 20 AU *p=*.009), week 10 (50 ± 21 AU) and week 16 (*p=*.003), and week 14 (50 ± 21 AU) to week 16 (*p=*.003).



Figure 6: EQ-5D-5L Utility Score and Visual Analogue Scale over 16 weeks with P Values.

*Functional Status*

PCFS at baseline was 2.7 ± 0.5 AU and improved relative to week 16 (2.3 ± 0.9 AU, *p*=<.001) and week 14 (2.4 ± 0.9 AU, *p*=.*011*). 6MWT at baseline was 365 ± 123m and was subsequently improved between baseline and week 16 (406 ± 141m *p<*.001) (Figure 7). Post-hoc analysis also demonstrated fright further improvements between week 4 and week 16 (*p=.*002*)*; and finally, week 8 and week 16 (*p=*.018). TUG was improved between baseline (7.2 ± 2.5s) and week 4 (6.7 ± 2.4s, *p=<.001)* and baseline to week 8 (6.5 ± 2.6s, *p=.016*) between baseline and week 12 (6.3 ± 2.6s, *p=<.002*) and between baseline and week 16 (6 ± 2.2s, *p=<.003*). There were no other between-timepoint changes.



Figure 7: PCFS, 6MWT, TUG over 16-weeks with P Values

*Physiological Measures*

MIP at baseline was 71 ± 26 cmH2O and was improved between baseline and week 16 (79 ± 28 cmH2O, *p*=.015). There was no significant change between any other time points for MIP or MEP**.** The global effect was significant for FEV1 (*p=*.003), FEV1/FVC (*p=*.045), and FVC (*p=*.001, Figure 8), however post hoc analysis showed no significance within pairwise comparisons. There was no significant difference in PEF across the 16 weeks. Blood panel results for a subset of 44 participants are presented in Table 2.



Figure 8: MIP, MEP, FEV1, FVC, FEV/FVC, PEF over 16-weeks with P Values.

Table 2: Blood Panel Results

|  |  |  |  |
| --- | --- | --- | --- |
| **N=44** | **Mean** | **Min** | **Max** |
| **WBC** (x10^9/L)Expected: 4.3-11(35) | 7.29 ± 1.99 | 4.10\* | 13.29\* |
| **RBC** (x10^12/L)Expected: 4.2-6.9(35) | 4.68 ± 0.54 | 2.83 | 5.77 |
| **Haemoglobin** (g-L)Expected: Males: 130-180 Females: 120-160(35) | 134.52 ± 16.67 | 67.00 | 169.00 |
| **Haematocrit** (%)Expected: Males 40-50, females 36-48(36) | 41 ± 4 | 22 | 50 |
| **MCV** (fL)Expected: 80-100(35) | 86.99 ± 7.30 | 65.10\* | 102.40\* |
| **MCH** (pG)Expected: 27-32(35) | 28.84 ± 2.93 | 19.80\* | 33.70\* |
| **MCHC** (g-L)Expected: 320-360(35) | 331.05 ± 11.97 | 300.00\* | 352.00 |
| **RDW** (%)Expected: 11.5-14.5%(37) | 13.01 ± 1.30 | 11.70 | 17.80\* |
| **Platelets** (x10^9/L)Expected: 150-400. (35) | 298.36 ± 57.52 | 200.00 | 439.00 |
| **Neutrophils** (x10^9/L)Expected: 1.8-7.8(35)% | 4.48 ± 1.6760.55 ± 8.22 | 2.3540.4 | 10.58\*79.6 |
| **Lymphocytes** (x10^9/L)Expected: 0.7-4.5(35)% | 2.09 ± 0.6729.27 ± 7.32 | 1.1513.50 | 4.4245.30 |
| **Eosinophils** (x10^9/L)Expected: 0-0.4(35)% | 0.13 ± 0.081.67 ± 0.87 | 0.010.1 | 0.49\*4.2 |
| **Monocytes** (x10^9/L)Expected: 0.1-1.0(35)% | 0.57 ± 0.158.00 ± 1.87 | 0.334.3 | 1.09\*13.3 |
| **Basophils** (x10^9/L)Expected: 0-0.2(35)% | 0.03 ± 0.010.41 ± 0.22 | 0.010.10 | 0.071.30 |
| **Ferritin** (ug-L)Expected: Males 30-300, females 10-200 (38) | 92.01 ± 100.15 | 0.98\* | 430.00\* |
| **D-Dimers** (ug-mL)Expected: 0.0-0.5(39) | 0.38 ± 0.29 | 0.00 | 1.85\* |
| **CRP** (mg L)Expected: <0.3(40) | 2.21 ± 3.63 | <0.01 | 19.0 |
| **LDH** (IU-L)Expected: 140-280(41) | 177.95 ± 20.90 | 121.00\* | 207.00 |
| Means, minimum and maximum values are presented with expected/standardised values. \*Data with a maximum or minimum value outside of expected values. |

**Discussion**

The key findings of this prospective cohort observation highlight the severity and frequency of Long COVID symptom profiles and how they impair quality of life and functional status via clinically relevant PROMs. Furthermore, the data demonstrates little/no improvement over sixteen weeks and the frequency of contact throughout the study demonstrates the episodic and relapsing nature of Long COVID. Data presented here should be used to help characterise Long COVID disability and to inform the development of Long COVID-specific guidelines and support services that can adequately respond to the observed reductions in all areas of patient wellbeing. To our knowledge, this is the first study to objectively collect biological, physiological, psychological, and cognitive parameters with regular frequency, and intensity. It is evident from the data across the patient profile, that performance in all areas of the study was well below expected clinically relevant ranges when compared to existing clinical and normative data sets. Here we provide a multi-dimensional insight into the characteristics/presentation of Long COVID, where previous data has been separated by prolonged periods where multiple remissions and changes in patient presentation are reported by patients but not captured. There is evidence of the episodic nature of Long COVID, which has been postulated and hypothesized in numerous patients' testimonies and accounts (42) but until now has not been demonstrated empirically via cross-sectional methodologies. The undulating/relapsing nature of fatigue, dyspnoea, and symptom profiles includes frequent and intense changes in symptom profiles. Thus, we provide evidence and a need for a distinct characterisation of Long COVID patients and their symptoms but also for personalised intervention approaches.

The burden of symptoms for patients demonstrates little/no progress towards pre-COVID-19 levels, although it is important again to highlight within-sample differences/heterogeneity across the measures/data. Throughout research on Long COVID, reports demonstrate that some, but not all patients improve over time. Still, there remains a level of uncertainty about whether those who are adversely affected by Long COVID expect a full recovery and return to pre-Long COVID status. This is important when considering the severity of reported disability and organ damage/insults that occur following infection with previous SARs-COV infections (43) and SARs-COV-2(44). In the context of Long COVID, a longitudinal cohort study conducted over 2 years found that only 7.6% (n=26) of participants fully recovered(45). Additionally, a multicentre, prospective cohort approach found that of 1170 patients hospitalised with COVID-19, only 29% (n=239) of individuals felt fully recovered and 20% (n=158) had a new disability 6 months later(46). Furthermore, it is reported that 59.8% of respondents (n=79) experienced one or more Long COVID symptoms in 6 months following the onset of acute COVID-19, decreasing to 53% at 12 months and increasing to 71.2% at 24 months(47). At twenty-four months the most frequent symptoms were fatigue (34.8%), amnesia (30.3%) and concentration difficulties (24.2%), which is like our findings where fatigue, concentration problems and memory loss were most prevalent across the 16 weeks. These studies highlight the importance of recognising the long-standing nature of Long COVID, as the knowledge gap of how patients present with high levels of variation demonstrates the need to understand various time points. A nationwide retrospective cohort study concluded that mild COVID-19 cases lead to a small number of health issues which are resolved within a year of diagnosis(48). Furthermore, this study reports that ‘mild’ cases do not lead to serious or chronic illness for most patients and therefore add only a minor continuous burden to the healthcare system(48). Within the study, patients infected with COVID-19 were matched to uninfected people, and hazard ratios were used to compare risks during the initial period of infection, and 180-360 days post-infection. This study was not complete using solely a Long COVID cohort, therefore the suggestion that individuals will not still be suffering at 12 months is not generalisable to Long COVID patients. Long COVID has been labelled the biggest mass-disabling event in history (49) and this study fails to acknowledge the struggles of those disabled by their Long COVID symptoms. The study discussed the frequently reported symptoms associated with Long COVID -19, but also used ‘seriousness is to quantify risk, and does not consider the impact of moderate-severe symptoms on an individual's quality of life.

In line with our findings, previous research has conceptualised Long COVID as an episodic illness, which is both multidimensional and unpredictable(42). Several longitudinal studies adopt methodologies to demonstrate the changes in symptom profiles and functional status from baseline to an end time point (3, 6, 12, 24 months) (11, 46-48, 50-54). However, to date methodologies that specifically observe and detail what happens between these time points are limited; therefore research regarding the high variation of symptoms beyond one point in time to better understand the episodic nature of Long COVID is vital to shaping support services that address the day-to-day challenges that patients experience. The fluctuating symptoms, relapse-remission cycles and reporting bias may overestimate recovery from Long COVID, particularly in studies with shorter follow-up periods or increased time lapses between assessments. The data here supports existing literature that highlights the severity, magnitude and undulating nature, of symptoms that can reduce the quality of life(55-59). Findings of health-related quality of life in patients 2 years post severe COVID-19 infection demonstrate a persistent worsened health status measured by the EQ-5D-5L(60). In agreement with existing literature(60), the mean utility index score for the EQ-5D-5L for our study was lower compared to population norms at baseline showing a reduced quality of life(61). Despite this and other variables significantly improving by week sixteen, we cannot conclude that this signifies recovery due to the non-linear trajectory and relapsing and remitting nature of Long COVID.

The highly cyclical symptom profiles and functional status of Long COVID further burden individuals and complicate their ability to plan and engage with typical life such as reducing individuals' work participation and social activities(62). Furthermore, the lingering and unpredictable nature of symptoms heavily impacts emotional state and challenges with emotional regulation, increases anxiety, hopelessness and depression as well as limiting daily functioning(63). Justified by the episodic nature of Long COVID considering the variation of symptom characteristics and severity, which is often exacerbated by periods of physical, mental and/or emotional exertion(44, 56, 64), uncertainty is a key theme across the Long COVID lived experience literature(9, 42, 65-67). The multidimensional nature of disability and fluctuations of episodic symptoms may vary over a day, and this unpredictability results in participants living and planning for one hour to the next(8). What is clear is that it remains a big challenge to address the broad and debilitating symptom profile. The research and findings here align with previous research that has identified the most prevalent symptom profiles associated with Long COVID and adds greater insight and evidence that characterises Long COVID as an episodic and disabling condition by demonstrating the frequent and intense changes that occur in the symptom profile and performance of patients. However, data here further outlines the integration of the symptoms with factors such as quality of life, and comparisons with healthy others and previous self, rather than considering these in isolation. For many participants, symptoms were managed by rest or sleep, which impacts their ability to undertake activities of daily life (i.e., completing the school run or engaging in social activities). It was reported that when participants did attempt activities that are deemed low intensity this would exacerbate symptoms and lead to an extended period of convalescence. Accordingly, attempting to live with Long COVID requires considered support mechanisms that aim to help individuals understand changes in their physical, mental, and emotional health which is in line with an episodic symptom profile that is prone to exacerbation. A further consideration is to understand the episodic nature of Long COVID. Participants here reported perceived improvements in symptom severity, often referring to ‘turning a corner’, however, this could change instantaneously and without any provocation in some cases, a finding that has been recognised in other studies(11, 57, 58, 68). It has been suggested that patients with chronic diseases will increase their activities when they feel able but with little consideration of the consequences(9). However, this does not align with our data which is better associated with the findings of Humphreys et al. (69) who report that Long COVID patients prioritise a sense of normality and control over relapse. Our findings indicate that pacing advice of activities seems to have become more widespread and useful through Long COVID clinics and television programmes since this work, yet specific guidelines are still scarce. As such, further research is required to document changes in symptom profiles relative to increased volume and intensity of activity.

There are many hypotheses for the underlying pathophysiology and mechanisms of Long COVID episodic nature. Still, there remains a dearth of literature that demonstrates efficacy in the form of pharmacological treatments that can be used to treat and address the complex and debilitating long-term outcomes that broadly impact people's lives(70). Cross-disciplinary conversations amongst relevant specialists commonly take place to discuss complex Long COVID cases, however despite this well-recognised approach, research suggests that its practicality in terms of service utilisation, patient outcomes (71) and patient experience (72) remains equivocal. Furthermore, there are currently no unified strategies in place to support patients with their uncertainties, or their daily struggles and reduced quality of life from undulating symptoms. Many patients will benefit from a complex tailored treatment approach, however, identifying patient profiles or phenotyping patients according to their symptom clusters may also present an additional challenge. Symptom clusters have been well-researched and accepted, however, there is limited research regarding the underlying mechanisms behind manifestations (73-77).Instead of varying pathogenically independent sub-syndromes, research observing sub phenotypes suggests additive severity of a single, multisystemic, multifaceted post-viral illness(45). Subsequently, there is a demand to develop approaches to phenotype relative to the underlying pathology and pathophysiology and clustering of symptoms rather than by the symptom presentation. Due to the broad, multi-system and complex profile of Long COVID, assessment and support services have been established which are underpinned by multi-disciplinary and integrated care approaches. Considering the evidence of adopting multi-disciplinary and integrated care, there is a need to devise substantive pathways that use coordinated, integrated whole-system thinking approaches(78). Further assessment tools and protocols are required urgently to inform the development of targeted, patient-centred, interdisciplinary support pathways, to restore functional capacity and quality of life.

A limitation of this research is that the heterogeneity in the sample is limited with most participants in this study Caucasian females. Within COVID-19 research, there is a lack of ethnic diversity, and representation of males, and young people, including children and young adults(56). Although the prevalence of self-reported Long COVID is greatest amongst females aged 35-69 years, ethnic minorities have been adversely affected by the COVID-19 pandemic(79-82), and there is a need for more representation within COVID-19 research. Additionally, the sample consists of individuals from a range of functional statuses identified using the PCFS tool. Whilst some participants corresponded to four on the PCFS, those with the most severe symptoms, such as being house/bed bound, would have been unable to complete the study therefore limiting the generalisability of the results.

**Conclusion**

Here, we demonstrate the long-term and broad range of issues affecting people living with Long COVID. Within this, we also demonstrate because of increased frequency and intensity of patient contact, the variable and episodic nature of Long COVID and the impact that this has on quality of life and functional status. Further research and sustained investment are needed to develop detailed Long COVID assessments that can inform targeted, patient-centred, interdisciplinary support pathways, which can be used alongside medicinal interventions to restore functional capacity and quality of life.

**Declarations:**

**Ethics approval and consent to participate**

NHS ethical approval (IRAS ID: 292920).

**Consent for publication**

Consent was provided by all participants prior to engagement.

**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding order on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

This study was supported by an unrestricted investigator-sponsored research grant from Gilead Sciences (#IN-UK-983-6080).

**Authors’ contributions**

MF and RA were co-principal investigators. MF, RA, TB, TMW, BEP and RJC conceptualised the research project. RO, CT, CK, TP, MF, RA, FVF and TMW were involved with data collection and supported analysis. RO, MF and RA were major contributors for writing and editing the manuscript. LS was the patient and public involvement and engagement (PPIE) representative. All authors read and approved the final manuscript.

**Acknowledgements**

The authors would like to acknowledge the contribution of our PPIE representatives who were and remain integral to our research.

**References:**

1. Johnson NP, Mueller J. Updating the accounts: global mortality of the 1918-1920 "Spanish" influenza pandemic. Bull Hist Med. 2002;76(1):105-15.

2. Løkke FB, Hansen KS, Dalgaard LS, Öbrink-Hansen K, Schiøttz-Christensen B, Leth S. Long-term complications after infection with SARS-CoV-1, influenza and MERS-CoV - Lessons to learn in long COVID? Infect Dis Now. 2023;53(8):104779.

3. Mao N, Zhang D, Li Y, Li Y, Li J, Zhao L, et al. How do temperature, humidity, and air saturation state affect the COVID-19 transmission risk? Environ Sci Pollut Res Int. 2023;30(2):3644-58.

4. Faghy MA, Owen R, Thomas C, Yates J, Ferraro FV, Skipper L, et al. Is long COVID the next global health crisis? J Glob Health. 2022;12:03067.

5. Fernandes Q, Inchakalody VP, Merhi M, Mestiri S, Taib N, Moustafa Abo El-Ella D, et al. Emerging COVID-19 variants and their impact on SARS-CoV-2 diagnosis, therapeutics and vaccines. Ann Med. 2022;54(1):524-40.

6. Nyberg T, Ferguson NM, Nash SG, Webster HH, Flaxman S, Andrews N, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. Lancet. 2022;399(10332):1303-12.

7. Thye AY, Law JW, Pusparajah P, Letchumanan V, Chan KG, Lee LH. Emerging SARS-CoV-2 Variants of Concern (VOCs): An Impending Global Crisis. Biomedicines. 2021;9(10).

8. O’Brien KK, Brown DA, McDuff K, Clair-Sullivan NS, Solomon P, Carusone SC, et al. Conceptualising the episodic nature of disability among adults living with Long COVID: a qualitative study. BMJ Global Health. 2023;8(3):e011276.

9. Wulf Hanson S, Abbafati C, Aerts JG, Al-Aly Z, Ashbaugh C, Ballouz T, et al. A global systematic analysis of the occurrence, severity, and recovery pattern of long COVID in 2020 and 2021. medRxiv. 2022.

10. Graham F. Daily briefing: At least 65 million people have long COVID. Nature. 2023.

11. Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. PLoS Med. 2021;18(9):e1003773.

12. Evans RA, Leavy OC, Richardson M, Elneima O, McAuley HJC, Shikotra A, et al. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. The Lancet Respiratory Medicine. 2022;10(8):761-75.

13. Taquet M, Skorniewska Z, Hampshire A, Chalmers JD, Ho L-P, Horsley A, et al. Acute blood biomarker profiles predict cognitive deficits 6 and 12 months after COVID-19 hospitalization. Nature Medicine. 2023;29(10):2498-508.

14. Raman B, McCracken C, Cassar MP, Moss AJ, Finnigan L, Samat AHA, et al. Multiorgan MRI findings after hospitalisation with COVID-19 in the UK (C-MORE): a prospective, multicentre, observational cohort study. The Lancet Respiratory Medicine. 2023;11(11):1003-19.

15. Klok FA, Boon GJAM, Barco S, Endres M, Geelhoed JJM, Knauss S, et al. The Post-COVID-19 Functional Status scale: a tool to measure functional status over time after COVID-19. European Respiratory Journal. 2020;56(1):2001494.

16. Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of Life Research. 2011;20(10):1727-36.

17. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54(7):581-6.

18. Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: The Fatigue Assessment Scale. Journal of Psychosomatic Research. 2003;54(4):345-52.

19. Larson RD. Psychometric properties of the modified fatigue impact scale. Int J MS Care. 2013;15(1):15-20.

20. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. Journal of the American Geriatrics Society. 2005;53(4):695-9.

21. Casanova C, Celli BR, Barria P, Casas A, Cote C, Torres JPd, et al. The 6-min walk distance in healthy subjects: reference standards from seven countries. European Respiratory Journal. 2011;37(1):150-6.

22. Chetta A, Aiello M, Foresi A, Marangio E, D'Ippolito R, Castagnaro A, et al. Relationship between outcome measures of six-minute walk test and baseline lung function in patients with interstitial lung disease. Sarcoidosis Vasc Diffuse Lung Dis. 2001;18(2):170-5.

23. Ubuane PO, Animasahun BA, Ajiboye OA, Kayode-Awe MO, Ajayi OA, Njokanma FO. The historical evolution of the six-minute walk test as a measure of functional exercise capacity: a narrative review. Journal of Xiangya Medicine. 2018;3.

24. Committee A. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-7.

25. Christopher A, Kraft E, Olenick H, Kiesling R, Doty A. The reliability and validity of the Timed Up and Go as a clinical tool in individuals with and without disabilities across a lifespan: a systematic review. Disabil Rehabil. 2021;43(13):1799-813.

26. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39(2):142-8.

27. McConnell A. Lung and respiratory muscle function. 2007. In: Sport and Exercise Physiology Testing Guidelines, the British Association of Sport and Exercise Sciences Guide [Internet]. Routledge; [63-76].

28. Program NAEaP. How to use a peak flow meter. How to use a metered-dose inhaler. 2013 [cited 2023. Available from: <https://www.nhlbi.nih.gov/health/public/lung/asthma/asthma_tipsheets.pdf>.

29. Koegelenberg CF, Swart F, Irusen EM. Guideline for office spirometry in adults, 2012. S Afr Med J. 2012;103(1):52-62.

30. Blanca MJ, Arnau J, García-Castro FJ, Alarcón R, Bono R. Non-normal Data in Repeated Measures ANOVA: Impact on Type I Error and Power. Psicothema. 2023;35(1):21-9.

31. Lee JH, Huber JC, Jr. Evaluation of Multiple Imputation with Large Proportions of Missing Data: How Much Is Too Much? Iran J Public Health. 2021;50(7):1372-80.

32. Rubin DB. Multiple imputation. Flexible Imputation of Missing Data, Second Edition: Chapman and Hall/CRC; 2018. p. 29-62.

33. Little RJ, Rubin DB. Statistical analysis with missing data: John Wiley & Sons; 2019.

34. Bennett DA. How can I deal with missing data in my study? Aust N Z J Public Health. 2001;25(5):464-9.

35. Khattak ZE, El Sharu H, Bhutta BS. Overview on Ordering and Evaluation of Laboratory Tests. StatPearls. Treasure Island (FL): StatPearls Publishing

Copyright © 2024, StatPearls Publishing LLC.; 2024.

36. Billett HH. Hemoglobin and Hematocrit. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. Boston: Butterworths

Copyright © 1990, Butterworth Publishers, a division of Reed Publishing.; 1990.

37. Said AS, Spinella PC, Hartman ME, Steffen KM, Jackups R, Holubkov R, et al. RBC Distribution Width: Biomarker for Red Cell Dysfunction and Critical Illness Outcome? Pediatr Crit Care Med. 2017;18(2):134-42.

38. Wang W, Knovich MA, Coffman LG, Torti FM, Torti SV. Serum ferritin: Past, present and future. Biochim Biophys Acta. 2010;1800(8):760-9.

39. Bounds EJ, Kok SJ. D Dimer. StatPearls. Treasure Island (FL): StatPearls Publishing

Copyright © 2024, StatPearls Publishing LLC.; 2024.

40. Nehring SM, Goyal A, Patel BC. C Reactive Protein. StatPearls. Treasure Island (FL): StatPearls Publishing

Copyright © 2024, StatPearls Publishing LLC.; 2024.

41. Farhana A, Lappin SL. Biochemistry, Lactate Dehydrogenase. StatPearls. Treasure Island (FL): StatPearls Publishing

Copyright © 2024, StatPearls Publishing LLC.; 2024.

42. Brown DA, O’Brien KK. Conceptualising Long COVID as an episodic health condition. BMJ Global Health. 2021;6(9):e007004.

43. Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364(14):1293-304.

44. O'Brien KK, Brown DA, Bergin C, Erlandson KM, Vera JH, Avery L, et al. Long COVID and episodic disability: advancing the conceptualisation, measurement and knowledge of episodic disability among people living with Long COVID – protocol for a mixed-methods study. BMJ Open. 2022;12(3):e060826.

45. Mateu L, Tebe C, Loste C, Santos JR, Lladós G, López C, et al. Determinants of the onset and prognosis of the post-COVID-19 condition: a 2-year prospective observational cohort study. The Lancet Regional Health – Europe. 2023;33.

46. Evans RA, McAuley H, Harrison EM, Shikotra A, Singapuri A, Sereno M, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. The Lancet Respiratory Medicine. 2021;9(11):1275-87.

47. Kim Y, Bae S, Chang H-H, Kim S-W. Long COVID prevalence and impact on quality of life 2 years after acute COVID-19. Scientific Reports. 2023;13(1):11207.

48. Mizrahi B, Sudry T, Flaks-Manov N, Yehezkelli Y, Kalkstein N, Akiva P, et al. Long covid outcomes at one year after mild SARS-CoV-2 infection: nationwide cohort study. BMJ. 2023;380:e072529.

49. Lieberwerth M, Niemeijer A. Lost and changed meaning in life of people with Long Covid: a qualitative study. International Journal of Qualitative Studies on Health and Well-being. 2024;19(1):2289668.

50. Taquet M, Skorniewska Z, Hampshire A, Chalmers JD, Ho L-P, Horsley A, et al. Acute blood biomarker profiles predict cognitive deficits 6 and 12 months after COVID-19 hospitalization. Nature Medicine. 2023;29(10):2498-508.

51. Cassar MP, Tunnicliffe EM, Petousi N, Lewandowski AJ, Xie C, Mahmod M, et al. Symptom Persistence Despite Improvement in Cardiopulmonary Health &#x2013; Insights from longitudinal CMR, CPET and lung function testing post-COVID-19. eClinicalMedicine. 2021;41.

52. McAuley HJC, Evans RA, Bolton CE, Brightling CE, Chalmers JD, Docherty AB, et al. Prevalence of physical frailty, including risk factors, up to 1 year after hospitalisation for COVID-19 in the UK: a multicentre, longitudinal cohort study. eClinicalMedicine. 2023;57.

53. Logue JK, Franko NM, McCulloch DJ, McDonald D, Magedson A, Wolf CR, et al. Sequelae in Adults at 6 Months After COVID-19 Infection. JAMA Network Open. 2021;4(2):e210830-e.

54. Vaes AW, Goërtz YMJ, Van Herck M, Machado FVC, Meys R, Delbressine JM, et al. Recovery from COVID-19: a sprint or marathon? 6-month follow-up data from online long COVID-19 support group members. ERJ Open Research. 2021;7(2):00141-2021.

55. Faghy MA, Maden-Wilkinson T, Arena R, Copeland RJ, Owen R, Hodgkins H, et al. COVID-19 patients require multi-disciplinary rehabilitation approaches to address persisting symptom profiles and restore pre-COVID quality of life. Expert Review of Respiratory Medicine. 2022:1-6.

56. Thomas C, Faghy MA, Owen R, Yates J, Ferraro F, Bewick T, et al. Lived experience of patients with Long COVID: a qualitative study in the UK. BMJ Open. 2023;13(4):e068481.

57. Wurz A, Culos-Reed SN, Franklin K, DeMars J, Wrightson JG, Twomey R. "I feel like my body is broken": exploring the experiences of people living with long COVID. Quality of Life Research. 2022.

58. Twomey R, DeMars J, Franklin K, Culos-Reed SN, Weatherald J, Wrightson JG. Chronic Fatigue and Postexertional Malaise in People Living With Long COVID: An Observational Study. Physical Therapy. 2022;102(4).

59. Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J Infect. 2020;81(6):e4-e6.

60. d’Ettorre G, Vassalini P, Coppolelli V, Gentilini Cacciola E, Sanitinelli L, Maddaloni L, et al. Health-related quality of life in survivors of severe COVID-19 infection. Pharmacological Reports. 2022;74(6):1286-95.

61. McNamara S, Schneider PP, Love-Koh J, Doran T, Gutacker N. Quality-Adjusted Life Expectancy Norms for the English Population. Value in Health. 2023;26(2):163-9.

62. Stelson EA, Dash D, McCorkell L, Wilson C, Assaf G, Re'em Y, et al. Return-to-work with long COVID: An Episodic Disability and Total Worker Health® analysis. Social Science & Medicine. 2023;338:116336.

63. Kennelly CE, Nguyen ATP, Sheikhan NY, Strudwick G, Ski CF, Thompson DR, et al. The lived experience of long COVID: A qualitative study of mental health, quality of life, and coping. PLOS ONE. 2023;18(10):e0292630.

64. Owen R, Ashton RE, Skipper L, Phillips BE, Yates J, Thomas C, et al. Long COVID quality of life and healthcare experiences in the UK: a mixed method online survey. Qual Life Res. 2023.

65. O’Brien KK, Brown DA, McDuff K, Clair-Sullivan NS, Solomon P, Carusone SC, et al. Conceptualising the episodic nature of disability among adults living with Long COVID: a qualitative study. BMJ Global Health. 2023;8(3):e011276.

66. Engwall M, Törnbom K, Persson HC, Palstam A. Recovering from COVID-19 - A Process Characterised by Uncertainty: A Qualitative study. J Rehabil Med. 2022;54:jrm00326.

67. Skilbeck L, Spanton C, Paton M. Patients' lived experience and reflections on long COVID: an interpretive phenomenological analysis within an integrated adult primary care psychology NHS service. J Patient Rep Outcomes. 2023;7(1):30.

68. O'Brien KK, Brown DA, McDuff K, St Clair-Sullivan N, Solomon P, Chan Carusone S, et al. Conceptualising the episodic nature of disability among adults living with Long COVID: a qualitative study. BMJ Glob Health. 2023;8(3).

69. Humphreys H, Kilby L, Kudiersky N, Copeland R. Long Covid and the role of physical activity: a qualitative study. medRxiv. 2020:2020.12.03.20243345.

70. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. Nature Reviews Microbiology. 2023.

71. Damery S, Flanagan S, Combes G. Does integrated care reduce hospital activity for patients with chronic diseases? An umbrella review of systematic reviews. BMJ Open. 2016;6(11):e011952.

72. Selby P, Popescu R, Lawler M, Butcher H, Costa A. The Value and Future Developments of Multidisciplinary Team Cancer Care. Am Soc Clin Oncol Educ Book. 2019;39:332-40.

73. Kenny G, McCann K, O'Brien C, Savinelli S, Tinago W, Yousif O, et al. Identification of Distinct Long COVID Clinical Phenotypes Through Cluster Analysis of Self-Reported Symptoms. Open Forum Infect Dis. 2022;9(4):ofac060.

74. Liu W, Liu J. Living with COVID-19: a phenomenological study of hospitalised patients involved in family cluster transmission. BMJ Open. 2021;11(2):e046128.

75. Fischer A, Badier N, Zhang L, Elbéji A, Wilmes P, Oustric P, et al. Long COVID Classification: Findings from a Clustering Analysis in the Predi-COVID Cohort Study. Int J Environ Res Public Health. 2022;19(23).

76. Raveendran AV, Jayadevan R, Sashidharan S. Long COVID: An overview. Diabetes Metab Syndr. 2021;15(3):869-75.

77. Sudre CH, Lee KA, Ni Lochlainn M, Varsavsky T, Murray B, Graham MS, et al. Symptom clusters in COVID-19: A potential clinical prediction tool from the COVID Symptom Study app. Science Advances. 2021;7(12):eabd4177.

78. Pronk NP, Faghy MA. Causal systems mapping to promote healthy living for pandemic preparedness: a call to action for global public health. International Journal of Behavioral Nutrition and Physical Activity. 2022;19(1):13.

79. Aldridge RW, Lewer D, Katikireddi SV, Mathur R, Pathak N, Burns R, et al. Black, Asian and Minority Ethnic groups in England are at increased risk of death from COVID-19: indirect standardisation of NHS mortality data. Wellcome Open Res. 2020;5:88.

80. Abedi V, Olulana O, Avula V, Chaudhary D, Khan A, Shahjouei S, et al. Racial, Economic, and Health Inequality and COVID-19 Infection in the United States. Journal of Racial and Ethnic Health Disparities. 2021;8(3):732-42.

81. Ekezie W, Maxwell A, Byron M, Czyznikowska B, Osman I, Moylan K, et al. Health Communication and Inequalities in Primary Care Access during the COVID-19 Pandemic among Ethnic Minorities in the United Kingdom: Lived Experiences and Recommendations. International Journal of Environmental Research and Public Health. 2022;19(22):15166.

82. Dennis A, Wamil M, Alberts J, Oben J, Cuthbertson DJ, Wootton D, et al. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. BMJ Open. 2021;11(3):e048391.

**Figure Captions**

**Figure 1:** A visual representation of the study and the activites completed by study participants.

**Figure 2:** Change in symptom scores across each timepoint. Hashed lined and P values represent significant changes between highlighted timepoints.

**Figure 3:** Symptom profiling across the duration of the study, colour coded to indicate severity and derived from the symptom burden questionnaire.

**Figure 4:** Panel plot demonstrating persistence of fatigue, breathlessness and cognitive function over the course of the study. Hashed lined and P values represent significant changes between highlighted timepoints.

**Figure 5:** Change in each domain of the Modified Fatigue Impact scale, across the study. Hashed lined and *P* values represent significant changes between highlighted timepoints.

**Figure 6:** Reported impact upon quality-of-life using the EQ-5D-5L and the EQ-5D-5L VAS score, hashed lined and *P* values represent significant changes between highlighted timepoints.

**Figure 7:** Panel plot demonstrating impaired functional status assessed by the Post COVID Functional Status Scale, Six Minute Walk Test and the Timed Up and Go. Hashed lined and P values represent significant changes between highlighted timepoints.

**Figure 8:** Panel plot profiling inspiratory and expiratory muscle strength and lung function data over the course of each face-to-face visit. Hashed lined and P values represent significant changes between highlighted timepoints.