

Examining Well-Being and Cognitive Function in People with Long COVID and ME/CFS, and Age-Matched Healthy Controls: A Case-Case-Control Study

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ABSTRACT

BACKGROUND: Well-being and cognitive function had not previously been compared between people with long COVID and people with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Therefore, this study examined well-being and cognitive function in people with long COVID (~16 months illness duration; n = 17) and ME/CFS (~16 years illness duration; n = 24), versus age-matched healthy controls (n = 16).

METHODS: Well-being was examined using several questionnaires, namely the Health Visual Analogue Scale (VAS), Fatigue Severity Scale (FSS), post-exertional malaise (PEM), Pittsburgh Sleep Quality Index (PSQI), European Quality of Life-5 Domains (EQ-5D), MRC Dyspnoea, Self-Efficacy (SELTC), The Edinburgh Neurosymptoms Questionnaire (ENS), General Anxiety Disorder 7 (GAD-7) and Patient Health Questionnaire 9 (PHQ-9). Cognitive function was examined using Single Digit Modalities Test (SDMT), Stroop test and Trails A and B. These were delivered via a mobile application (app) built specifically for this remote data collection.

RESULTS: The main findings of the present investigation were that people with ME/CFS and people with long COVID were generally comparable on all well-being and cognitive function measures, but self-reported worse values for pain, fatigue, post-exertional malaise, sleep quality, general well-being in relation to mobility, usual activities, self-care, breathlessness, neurological symptoms, self-efficacy and other well-being such as anxiety and depression, compared to controls. There was no effect of group for cognitive function measures.

CONCLUSIONS: These data suggest that both people with long COVID and people with ME/CFS have similar impairment on well-being measures examined herein. Therefore, interventions that target well-being of people with ME/CFS and long COVID are required.

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KEYWORDS: Chronic fatigue syndrome; Cognitive function; Long COVID; Myalgic encephalomyelitis; Post-exertional malaise; Well-being

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INTRODUCTION

Individuals with symptoms from 4 to >12 weeks post-acute COVID-19 infection are considered to have long COVID according to the NICE guidelines.¹ Long COVID is a condition characterised by over 100 symptoms ranging from muscle pain to severe fatigue and has multiple overlaps with ME/CFS.² ME/CFS is a debilitating condition, and individuals with ME/CFS report symptoms from severe fatigue to cognitive impairment,³ analogous to long COVID. Some studies have compared individuals with long COVID, ME/CFS and healthy matched controls for mobility,⁴ vascular function,⁵ complex post-traumatic stress disorder (CPTSD)/post-traumatic stress disorder (PTSD)⁶ and dexterity and bimanual coordination.⁷ Findings from these studies highlight individuals with long COVID and ME/CFS face comparable vascular and mobility impairments, greater prevalence of both CPTSD and PTSD, and impaired dexterity and bimanual coordination compared to controls.^{4-6,8} Studies concerning well-being and cognitive function in individuals with long COVID and ME/CFS have considered each patient group in isolation⁹⁻¹² so uncertainty remains whether individuals with long COVID and ME/CFS differ on well-being and cognitive function measures.

Past studies demonstrate that individuals with long COVID and ME/CFS report pain, fatigue, post-exertional malaise, sleep disturbances, breathlessness and neurological abnormalities.^{2,13-25} Pain, namely musculoskeletal pain, is reportedly the most common persistent symptom in long COVID,¹³ and most (68%) commonly reported pain in CFS.¹⁴ Fatigue is a dominant feature of long COVID with 46% of patients reporting fatigue that lasts from weeks to months,¹⁵ and ME/CFS is a long-term condition characterised by extreme fatigue worsened by exertion.¹⁶ Post-exertional malaise is a debilitating period following physical and/or cognitive exertion in both long COVID and ME/CFS.^{17,18} About 59% of people with long COVID met the post-exertional malaise threshold used in people living with ME/CFS,¹⁷ and post-exertional malaise is known to be one of the defining features of ME/CFS.¹⁸ Poor sleep quality is another common symptom, experienced by 65% of previously acute COVID-19 patients.¹⁹ In individuals with ME/CFS, a non-restorative sleep despite extended or sufficient total sleep time is one of the major clinical diagnostic criteria.²⁰ Persistent breathlessness has been identified as a highly debilitating post-COVID-19 symptom.²¹ In a study by Kim et al.²² they identified a potential association of small airway functional impairment

with breathlessness in long COVID. Individuals with ME/CFS also reported breathlessness following exertion.²³ Neurological abnormalities are present in both patient groups, and Pilotto et al²⁴ found that at neurological examination, 40% of hospitalised and non-hospitalised COVID-19 patients exhibited neurological abnormalities, and there is accumulating evidence of neurological dysfunction in ME/CFS.²⁵

Previous literature also suggests lower health-related quality of life in previous acute COVID-19 patients,²⁶ and in individuals with ME/CFS compared to the population mean.²⁷ Symptoms of anxiety and depression have been reported in people 3 months post-COVID-19 infection, but whether this remains manifest in long COVID is unknown.²⁸ Means-Christensen et al²⁹ found a relationship between pain, anxiety and depression supporting previous observations in both long COVID and ME/CFS, as both conditions report pain as the most persistent symptom.^{13,14} A

systematic review and meta-analysis revealed that around half of ME/CFS patients experience anxiety and/or depression.³⁰ Self-efficacy is one measure that has not previously been explored in individuals with long COVID and ME/CFS. Self-efficacy refers to a belief in one's capacity to act in ways to attain goals³¹ which might be lower in people with long COVID and ME/CFS given extraneous factors out of one's control such as symptoms or sudden post-exertional malaise, which can limit one from achieving intended goals.

Individuals with long COVID and ME/CFS report cognitive deficits or abnormalities, and long COVID patients (laboratory tested and positive) performed worse in attention and working memory cognitive tasks.³² In a meta-analysis conducted by Sebaiti et al,¹² it was revealed that impairments affected visuo-spatial immediate memory, reading speed, graphic gestures, difficulties in several processes in episodic verbal memory, and visual memory in individuals with ME/CFS.

To the best of our knowledge, no previous studies have compared individuals with long COVID, ME/CFS and healthy controls on these aforementioned measures of well-being and cognitive function. We hypothesised individuals with long COVID and ME/CFS would display similar levels of impairment in all their well-being and cognitive function measures. Moreover, we hypothesised both patient groups would display worse well-being and cognitive function outcomes compared to the age-matched healthy controls.

CLINICAL SIGNIFICANCE

- Long COVID and ME/CFS cause impaired well-being and cognitive function, putting these groups at greater risk of employment and activities of daily living challenges.
- People with Long COVID and ME/CFS have lower well-being but comparable cognitive function when compared to controls, which likely causes greater dysfunction in their daily lives.
- As a result, accommodations for activities of daily living should be made available to long COVID and ME/CFS individuals.

METHODS

Participants

Fifty-seven participants (long COVID, $n = 17$; ME/CFS, $n = 24$; and healthy controls, $n = 16$, Table) were recruited for this study via social media using Facebook/Meta and Twitter/X. Participants took part in the study between June 2022 and March 2023. This study was carried out in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee. Written informed consent was obtained from all participants in the app prior to completion of all questionnaires.

Materials and Apparatus

All well-being measures were self-reported on a mobile application (app). Pain was measured using the Health Visual Analogue Scale (VAS) on a scale from 0 (no pain at all) to 100 (worst pain imaginable).³³ Fatigue was measured using the 9-item Fatigue Severity Scale (FSS) on a 1 (strongly disagree) to 7 (strongly agree) scale.³⁴ The DePaul symptom questionnaire was used to grade post-exertional malaise.³⁵ The total score ranged from 0 to 2000

for frequency and severity of post-exertional malaise. Frequency was rated on a scale from 0 (none of the time) to 4 (all of the time), and severity was rated on a scale from 0 (symptom not present) to 4 (very severe). The Pittsburgh Sleep Quality Index (PSQI) measured sleep quality and disturbance over a 1-month period using self-reports to rate 7 areas of sleep on a 0 to 3 (extreme) scale.³⁶ Breathlessness/dyspnoea was measured using the MRC Dyspnoea, this questionnaire graded breathlessness/dyspnoea against the ability to carry out activities of daily living on a scale from 0 to 3.³⁷ Neurological function was measured using the Edinburgh Neurosymptoms Questionnaire (ENS). This 30-item survey assessed the presence and nature of blackouts, weakness, hemisensory syndrome, memory problems, tremor, pain, fatigue, globus and multiple medical problems.³⁸ Quality of life was measured using the European Quality of Life with 5 domains (EQ-5D), anxiety/depression, mobility, pain, self-care and activity, and these dimensions were graded on a Likert scale from 0 to 4.³⁹ Anxiety symptoms were measured using the 7-item General Anxiety Disorder 7 (GAD-7) scale on a 0 (not at all) to 3 (nearly every day) scale.⁴⁰ Depression symptoms were measured using the Patient Health Questionnaire 9 (PHQ-9) with

Table Descriptive Data of Participants

Variable	Group	Mean	SD	ANOVA <i>P</i> Value for Effect of Group
Age (years)	LC ($n = 17$)	47	10	0.8278 (LC vs ME/CFS)
	ME/CFS ($n = 24$)	50	10	<0.0001 (LC vs controls) [#]
	Control ($n = 16$)	53.6	13	<0.0001 (ME/CFS vs controls) [#]
Height (cm)	LC ($n = 17$)	168	10	0.9268 (LC vs ME/CFS)
	ME/CFS ($n = 24$)	169	9	0.8259 (LC vs controls)
	Control ($n = 16$)	170	9	0.9700 (ME/CFS vs controls)
Body mass (kg)	LC ($n = 17$)	99	23	0.2212 (LC vs ME/CFS)
	ME/CFS ($n = 24$)	87	25	0.0012 (LC vs controls) [†]
	Control ($n = 16$)	71	16	0.0879 (ME vs controls)
BMI (kg/m ²)	LC ($n = 17$)	35	6	0.2881 (LC vs ME/CFS)
	ME/CFS ($n = 24$)	31	9	0.0002 (LC vs controls) [‡]
	Control ($n = 16$)	24	4	0.0127 (ME/CFS vs controls) [*]
Systolic blood pressure (mmHg)	LC ($n = 17$)	145	18	0.3670 (LC vs ME/CFS)
	ME/CFS ($n = 24$)	136	19	0.5690 (LC vs controls)
	Control ($n = 16$)	138	21	0.9558 (ME/CFS vs controls)
Diastolic blood pressure (mmHg)	LC ($n = 17$)	96	14	0.0491 (LC vs ME/CFS) [*]
	ME/CFS ($n = 24$)	86	12	<0.0001 (LC vs controls) [#]
	Control ($n = 16$)	77	8	0.0724 (ME/CFS vs controls)
Resting heart rate (bpm)	LC ($n = 17$)	81	14	0.9781 (LC vs ME/CFS)
	ME/CFS ($n = 24$)	80	18	0.0183 (LC vs controls) [*]
	Control ($n = 16$)	66	10	0.0215 (ME/CFS vs controls) [*]

LC = long COVID; ME/CFS = myalgic encephalomyelitis/ chronic fatigue syndrome.

* $P < .05$.

† $P < .01$.

‡ $P < .001$.

$P < .0001$.

scores ranging from 0 (not at all) to 3 (nearly every day).⁴¹ Self-efficacy was measured using the Self-Efficacy (SELTC) questionnaire assessing self-efficacy on 3 subscales; 5-item self-efficacy pain subscale, 9-item self-efficacy function subscale and 6-item self-efficacy in other symptoms subscale rated on a 10 (very uncertain) to 100 (very certain) scale.⁴²

Single Digit Modalities Test (SDMT) measured number of correctly identified shapes and time to completion.⁴³ Participants match 49 shapes on the screen to numbers from 1 to 10 grid at the top of the screen. The Stroop test assessed users' response rates on ten congruent (pound signs presented in red, green, or blue and correct response would be the matching colour) and incongruent stimuli (word green is displayed in red colour and correct response is red).⁴⁴ Trails A and B measured psychomotor speed, visual search and attention. Part A required the participant to connect 25 randomly placed circles in ascending numerical order, and part B required the participant to connect 24 randomly placed circles in ascending order, alternating between numbers and letters. The test was scored based on completion duration.⁴⁵

Statistical Analysis

Data were analysed using Jamovi (Version 2.3.21) and figures were created using GraphPad Prism (Version 9.4.1). To assess the differences across dependent variables, Welch's one-way analyses of variance (ANOVA) were performed. All data were assessed for normal distribution and homogeneity of variance using Shapiro-Wilk's and Levene's tests, respectively. Where data violated assumptions, non-parametric equivalents were used. Effect size for paired comparisons was conducted using Cohen's d whereby the difference in means between 2 samples was divided by the pooled standard deviation (SD). Thresholds of 0.2, 0.5 and 0.8 correspond to small, moderate and large effects for Cohen's d .⁴⁶ Data are presented with alpha levels reported as exact P values. For figures, data are presented as mean \pm SD and individual data points as recommended by Drummond and Vowler.^{47,48} Where data were not normally distributed, figures present data as median (interquartile range [IQR]).

RESULTS

General Health

Health VAS (Figure 1A) was lower in long COVID ($d = -3.176$), and ME/CFS ($d = -2.596$) than controls and not different between long COVID and ME/CFS ($d = 0.580$).

Fatigue

FSS (Figure 1B) scores were higher in long COVID than controls ($d = 6.045$); and between ME/CFS vs controls ($d = 5.696$). There was no between group difference for long COVID vs ME/CFS ($d = -0.349$).

Post-Exertional Malaise

Post-exertional malaise frequency (Figure 1C) was higher in both long COVID ($d = 2.789$) and ME/CFS ($d = 2.047$) vs controls, but was similar between long COVID and ME/CFS ($d = -0.742$). Post-exertional malaise severity (Figure 1D) was higher in both long COVID ($d = 1.757$) and ME/CFS ($d = 1.526$) vs controls, but similar between long COVID and ME/CFS groups ($d = -0.231$).

Sleep Quality

PSQI scores (Figure 1E) were higher in long COVID ($d = 1.090$) and ME/CFS ($d = 1.236$) than controls. No difference between long COVID and ME/CFS existed ($d = 0.146$).

Mobility

EQ5D revealed that mobility issues (Figure 1F) were similar between long COVID and ME/CFS ($d = -0.053$), and both groups had greater mobility issues compared to controls ($d = 2.273$ and $d = 2.220$).

Usual Activities

Long COVID ($d = 3.021$) and ME/CFS ($d = 2.041$) reported more problems with usual activities in the EQ5D (Figure 1G) compared to controls. Usual activity scores were similar between long COVID and ME/CFS ($d = -0.613$).

Self-Care

Problems with self-care were similar between long COVID and ME/CFS (Figure 1H: $d = 0.089$) and were both higher when compared to controls ($d = 1.232$ and $d = 1.322$).

Pain

The EQ5D questionnaire showed long COVID and ME/CFS groups report higher pain and discomfort than controls (Figure 1I: $d = 1.713$ and $d = 1.780$). Pain was similar between long COVID and ME/CFS ($d = 0.066$).

Dyspnoea

Dyspnoea in the MRC questionnaire (Figure 1J) was higher in long COVID and ME/CFS compared to controls ($d = 2.024$ and $d = 1.726$). Breathlessness was similar between long COVID and ME/CFS ($d = -0.298$).

Self-Efficacy

SELTC revealed self-efficacy (Figure 1K) to be similar between long COVID and ME/CFS ($d = 0.023$), with both groups reporting lower self-efficacy than controls ($d = -2.812$ and $d = -2.789$).

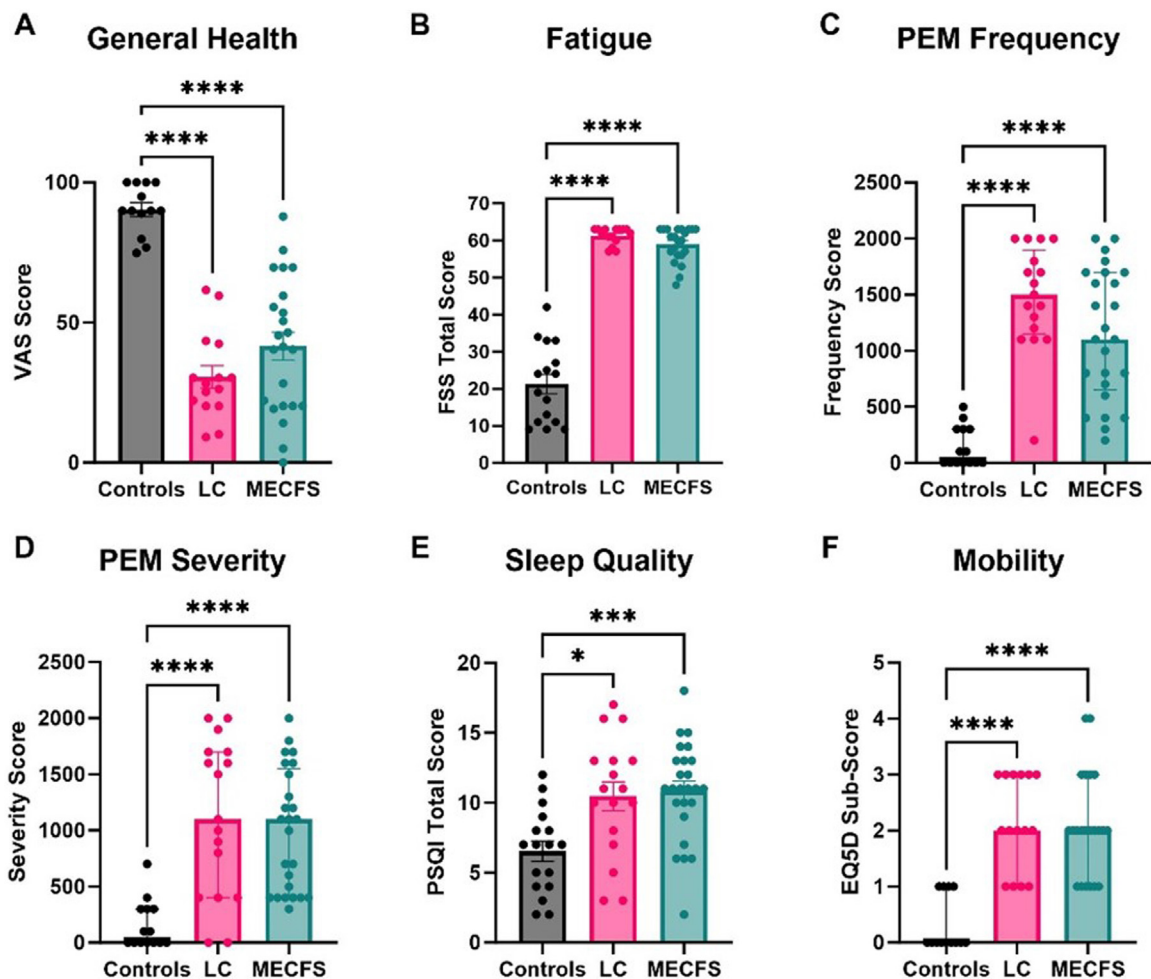


Figure 1 Health and well-being outcomes, including general health (A), fatigue (B), post-exertional malaise frequency (C) and severity (D), sleep quality (E), mobility (F), usual activities (G), self-care (H), pain/discomfort (I), dyspnoea (J), self-efficacy (K), neurological symptoms (L), anxiety (M), depression (N), and anxiety & depression (O). Normally distributed data are presented as mean \pm SD (A, B, E, J, K, M, N). Data which were not normally distributed have been presented as median (IQR) (C, D, F-I, L, O). Individual data points displayed. Long COVID (n = 17), ME/CFS, (n = 24), Controls (n = 16). ** $P < .01$, *** $P < .001$, **** $P < .0001$.

Neurological Symptoms

Neurological symptoms, as assessed by EDNS (Figure 1L), were higher in long COVID vs controls ($d = 2.608$) and ME/CFS vs controls ($d = 2.998$). There were no difference between long COVID and ME/CFS ($d = 0.390$).

Anxiety and Depression

GAD7 (Figure 1M) revealed higher anxiety in ME/CFS than controls ($d = 0.937$), no differences between long COVID vs controls ($d = 0.834$), or between long COVID and ME/CFS ($d = 0.103$). PHQ-9 depression scores (Figure 1N) were higher in long COVID than controls ($d = 2.610$) and in ME/CFS compared to controls ($d = 2.189$), but no difference existed between long COVID and ME/CFS ($d = -0.422$). EQ5D (Figure 1O) anxiety and depression scores were higher in long COVID and ME/CFS compared to controls ($d = 1.474$ and $d = 1.189$), without

differences between long COVID and ME/CFS ($d = -0.285$).

Cognitive Function

SDMT scores were similar across all 3 groups (Figure 2A; long COVID vs controls: $d = 0.399$; ME/CFS vs controls: $d = 0.464$; long COVID vs ME/CFS: $d = 0.065$). Stroop test results revealed that all 3 groups scored similarly with the total number correct (Figure 2B; long COVID vs controls: $d = 0.047$; ME/CFS vs controls: $d = 0.091$; long COVID vs ME/CFS: $d = 0.044$). The total time to complete the Stroop test was also similar across groups (Figure 2C; long COVID vs controls: $d = 0.676$; ME/CFS vs controls: $d = 0.715$; long COVID vs ME/CFS: $d = 0.039$). Trials A completion time was similar across the 3 comparison groups (Figure 2D; long COVID vs controls: $d = 0.547$; ME/

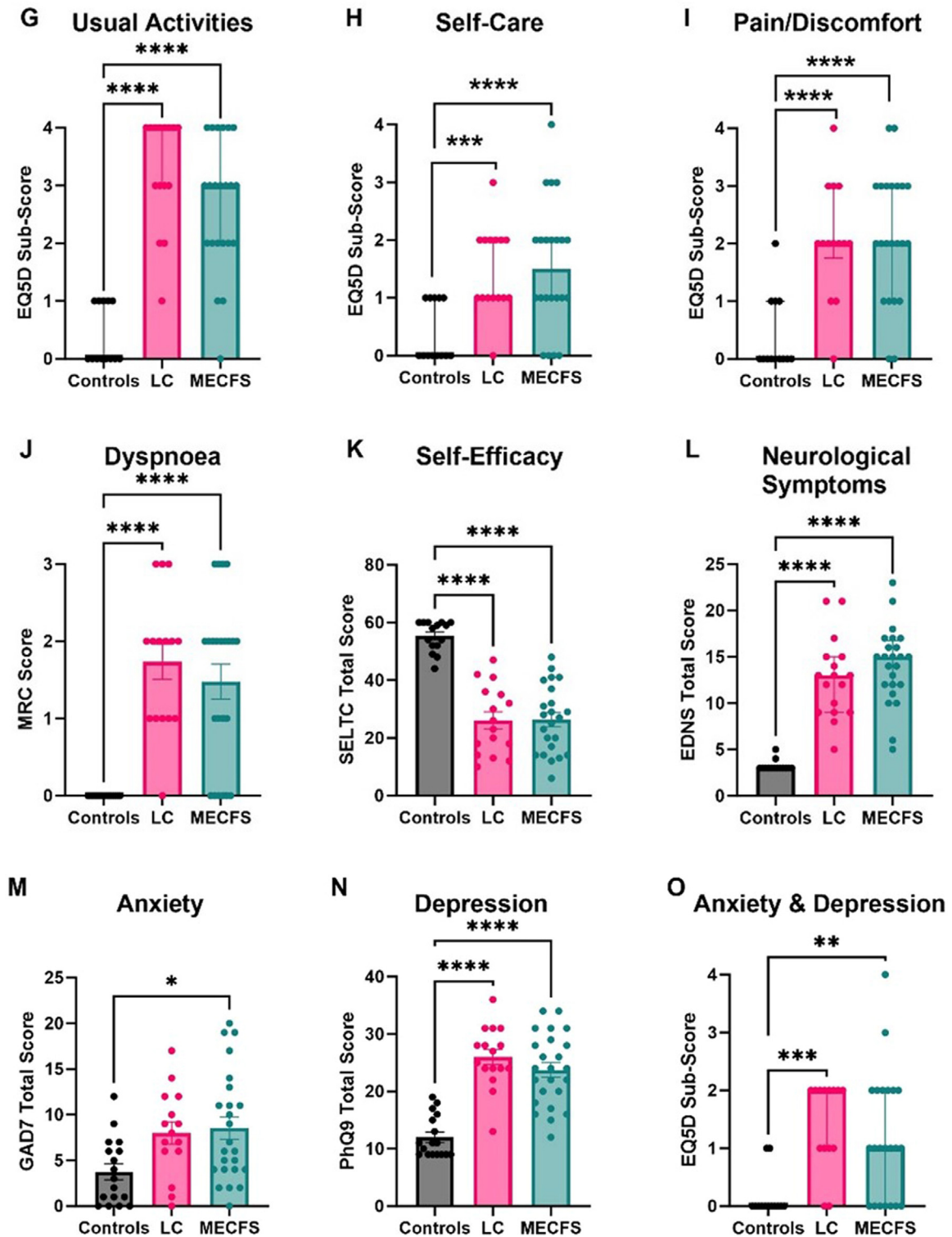


Figure 1 Continued.

CFS vs controls: $d = 0.166$; long COVID vs ME/CFS: $d = 0.547$). Likewise, Trails B completion time was similar across the 3 comparison groups (Figure 2E; long COVID vs controls: $d = 0.113$; ME/CFS vs controls: $d = 0.305$; long COVID vs ME/CFS: $d = 0.192$).

DISCUSSION

The aim of this study was to compare people with long COVID, ME/CFS and age-matched healthy controls on well-being and cognitive function measures. The main findings of the present investigation highlight the comparability

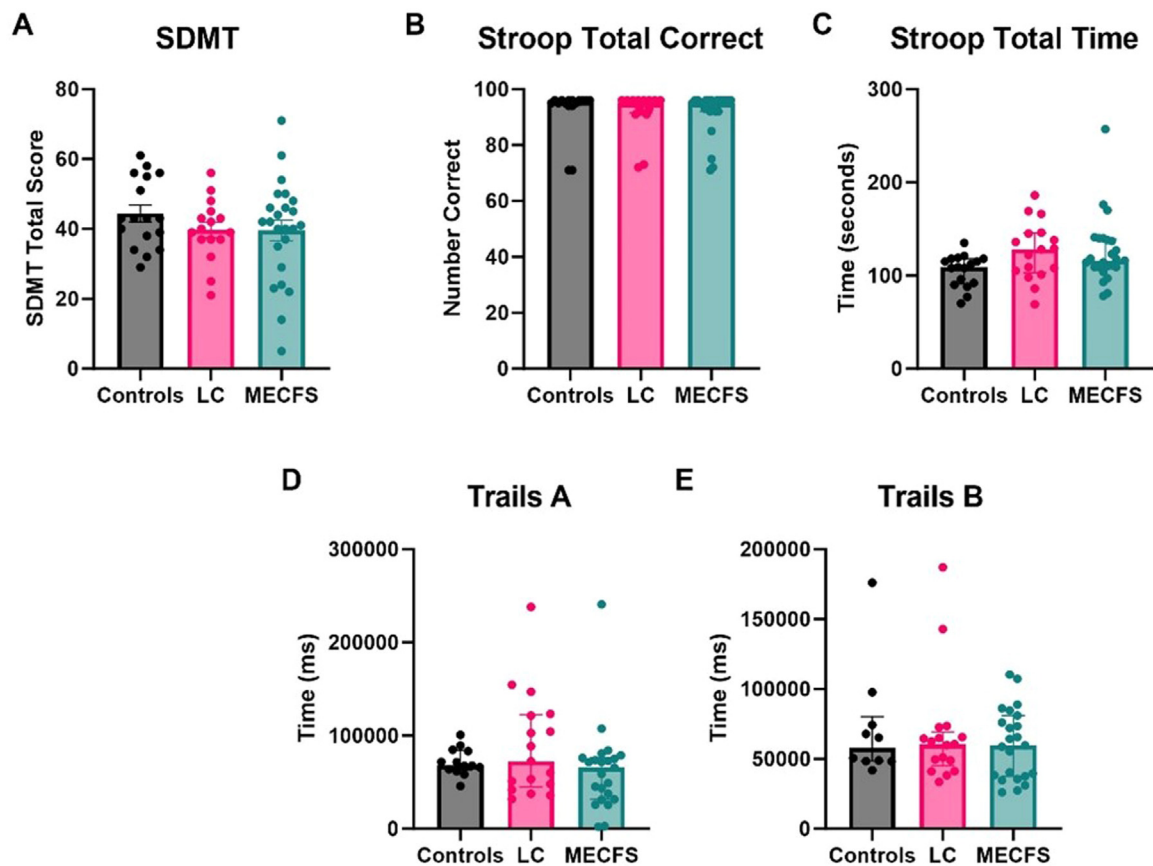


Figure 2 Cognitive outcomes, including Single Digit Modalities Test (SDMT); (A), Stroop Total Correct (B), Stroop Total Time (C) Trails A (D) and B (E). Normally distributed data are presented as mean \pm SD (A). Data which were not normally distributed have been presented as median (IQR) (B-D). Individual data points displayed. Long COVID (n = 17), ME/CFS, (n = 24), Controls (n = 16).

between individuals with long COVID and ME/CFS on well-being and cognitive function measures. Moreover, both patient groups self-reported worse values compared to controls for the well-being measures; pain, fatigue, post-exertional malaise, sleep quality, general well-being on mobility, usual-activities, self-care, breathlessness, neurological symptoms and self-efficacy, anxiety and depression. These findings were in line with our hypotheses. Interestingly, both patient groups did not differ in their cognitive function compared to controls, which was contrary to our hypotheses.

Our well-being findings support existing literature that individuals with long COVID and ME/CFS report pain,^{13,14} fatigue,^{15,16} post-exertional malaise,^{17,18} poor sleep,^{19,20} breathlessness,²¹⁻²³ neurological abnormalities,^{24,25} lower quality of life,^{26,27} symptoms of anxiety and depression,^{29,30} and self-efficacy.³¹ Existing literature highlights that pain is reported by both long COVID and ME/CFS patient groups;^{13,14} fatigue is reported to be a dominant feature of both conditions;^{15,16} post-exertional malaise is reported to be a debilitating period after physical and cognitive exertion in both long COVID, and ME/CFS;^{17,18} poor sleep quality is reported to be a very common

symptom experienced by individuals with long COVID, and ME/CFS;^{19,20} breathlessness is reported to be a highly debilitating symptom in both long COVID and following exertion in ME/CFS;²¹⁻²³ neurological abnormalities are present in both patient groups;^{24,25} quality of life is reported to be lower among individuals with long COVID and ME/CFS compared to the population mean,^{26,27} and both individuals with long COVID and ME/CFS report symptoms of depression and anxiety.^{29,30} In terms of self-efficacy, previous research has generally considered self-efficacy in regards to the COVID-19 pandemic,³¹ thus our findings presented herein are novel and have implications for the long COVID population.

Our cognitive function findings do not support the existing literature that suggest cognitive impairment, deficits and abnormalities in people with ME/CFS and long COVID.^{12,32} Past research on cognitive function in long COVID and ME/CFS highlight that individuals with long COVID performed worse in cognitive tasks related to attention and working memory,³² and individuals with ME/CFS exhibited impairments affecting various cognitive processes involved in episodic verbal memory, and visual memory.¹² We assessed cognitive function using following cognitive tasks: SDMT, the Stroop test and Trails A and B

that capture these affected cognitive processes in individuals with long COVID, and ME/CFS.¹² In the present study, we presented these tasks on a mobile device app which involved moving fingers to form trails or clicking on correct answers on a small screen. Therefore, it is possible that the nature of the task in the present study may have been less challenging in terms of dexterity and force application than in a typical experimental setting on a large keyboard. This is an important finding and should be considered going forwards when testing cognitive function in people with impaired dexterity (as in our patient groups),⁷ so researchers do not conflate poor dexterity with poorer cognitive function.

Limitations

This study acknowledges specific limitations that deserve acknowledgment. Firstly, the sample size was relatively small, and was not powered to detect changes in all outcomes at the $P < .05$ level. However, to mitigate this limitation, we have presented magnitude-based inferences throughout for readers to interpret findings using statistical philosophy. Secondly, findings herein were self-reported, so caution must be applied when interpreting findings, as they may be subject to biases and inaccuracies inherent in individuals' perceptions and recollections (e.g., recall bias). Thirdly, the observed magnitude of the well-being and cognitive function measures in this study likely underestimates the true effects when compared to controls because this paper was a small part of a larger project which involved participants attending the laboratory. As such, we acknowledge the inherent selection bias as only the least ill participants would be able to attend to laboratory for testing.

CONCLUSION

Comparisons of well-being and cognitive function measures amongst individuals with long COVID, ME/CFS and healthy controls herein present a novel approach for establishing and defining similarities and differences between these conditions. Long COVID is a new condition, whereas ME/CFS is a condition dating back decades,⁴⁹ so for that reason it is important to contrast these conditions in both well-being and cognitive function measures. In summary, results of this study demonstrate that both people with long COVID and people with ME/CFS exhibit similarly low well-being measures. It is therefore evident, that these post-viral conditions exert a significant burden on people with long COVID and ME/CFS and well-being of these groups must be prioritised when developing intervention strategies to treat or manage said conditions.

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