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CLINICAL RESEARCH STUDY

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People with Long Covid and ME/CFS Exhibit Similarly Impaired Balance and Physical Capacity: A Case-Case-Control Study

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ABSTRACT

PURPOSE: Postural sway and physical capacity had not previously been compared between people with long COVID and people with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Therefore, this study determined postural sway and physical capacity in people with long COVID (~16-month illness duration; n = 21) and ME/CFS (~16-year illness duration; n = 20), vs age-matched healthy controls (n = 20).

METHODS: Postural sway was during a 30-s static stand test. Physical capacity was determined using the Timed Up and Go test and 5 Times Sit to Stand test. Throughout, participants wore isoinertial measurement units.

RESULTS: Postural sway was worse (ie, greater) in people with long COVID and ME/CFS than controls, but not different between long COVID and ME/CFS. Performance of the Timed Up and Go test and 5 Times Sit to Stand test were worse in long COVID and ME/CFS than controls, but not different between long COVID and ME/CFS. Of long COVID and ME/CFS participants, 87% and 13% exceeded the threshold for muscle weakness in the 5 Times Sit to Stand test and Timed Up and Go test, respectively.

CONCLUSIONS: These data suggest that both people with long COVID and people with ME/CFS have similarly impaired balance and physical capacity. Therefore, there is an urgent need for interventions to target postural sway and physical capacity in people with ME/CFS, and given the current pandemic, people with long COVID.

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KEYWORDS: Balance; Chronic fatigue syndrome; Functional capacity; Myalgic encephalomyelitis; Post-exertional malaise; Postural control

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INTRODUCTION

Post-viral illness occurs when individuals experience an extended period of feeling unwell and fatigued after a viral infection.[1-3] Long COVID, which has been defined by the National Institute for Health and Care Excellence guidelines as symptoms ongoing from 4 weeks to over 12 weeks post-acute infection has put a spotlight on post-viral fatigue in the last 3 years. Long COVID is a term used to describe a constellation of symptoms that persist beyond the acute phase of COVID-19.[4,5] Multiple symptoms are manifest in post-viral illnesses,[6-8] with our recent systematic review reporting up to 56% prevalence of mobility problems, up to 64% prevalence of decreased functional status, and up to 100% prevalence of sensory impairments in people following acute COVID-19 infection.[3] Although long COVID is a relatively new condition, myalgic encephalomyelitis (ME), chronic fatigue syndrome (CFS), or ME/CFS has been evident in the medical literature for decades,[9] and has multiple overlaps with long COVID.[10,11] ME/CFS is a debilitating condition characterized by severe fatigue, cognitive impairment, and a host of other symptoms, with no known cure or definitive treatment.[12-14] Neurological effects of both long COVID and ME/CFS are commonly described in the medical literature.[10,13,15,16] In this context, several mechanisms concerning how ME/CFS affects the nervous system have been theorized, including autonomic nervous system dysfunction,[17] neuroendocrine disorder (particularly the hypothalamic-pituitary-adrenal axis),[18] and immune system abnormalities[19] (which result in the increased production of pro-inflammatory cytokines, ultimately causing neuroinflammation).[20] Interestingly, research concerning long COVID has also identified autonomic nervous system dysfunction,[21] neuroendocrine abnormalities (particularly the hypothalamic pituitary adrenal axis),[22] and immune system abnormalities,[23] leading to neuroinflammation.[24]

CLINICAL SIGNIFICANCE

- Long COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) cause postural instability, putting these groups at greater risk of future falls.
- People with long COVID and ME/CFS have lower physical capacity than controls, which likely causes greater fatigue in their daily lives.
- As a result of the above, rehabilitation programs should be implemented, or accommodations for activities of daily living and employment should be made for people with long COVID and ME/CFS.

The nervous system is responsible for coordinating appropriate postural control, through sensory input, integration, motor output, feedback control, or reflexes.[25-29] As a result, both conditions (ME/CFS and long COVID) may lead to impaired balance, postural control, and physical capacity.[30-34] Indeed, such findings have been reported in both people with long COVID[31,35] and people with ME/CFS.[36] Most of the literature concerning balance in people with ME/CFS, however, concerns disequilibrium on standing resultant from orthostatic intolerance.[37-39] In fact, we are aware of only one study that has examined balance in people with ME/CFS not using disequilibrium to determine orthostatic intolerance.[36] This is surprising, as balance problems are a commonly cited symptom by patients, and used as diagnostic criteria within the literature.[40,41] Serrador et al[36] examined balance in people with ME/CFS during static balance tasks and reported that people with ME/CFS have poorer postural control (ie, more sway) than healthy controls. These authors subsequently asked participants to self-report physical capacity and noted a significant correlation between balance performance and physical capacity, emphasizing the importance of postural control for physical capacity and activities of daily living.

Humans have long been known to exhibit postural sway during standing.[42,43] Postural sway is characterized by oscillating body movements, primarily observed during quiet stance. Postural sway is most commonly attributed to errors, or delays, in the postural control system, whereby visual, vestibular, and proprioceptive cues are continuously integrated to guide postural motor behaviour.[29,44,45] Consequently, postural sway measures have often been used as a measure of balance ability, particularly in older adults, and have been associated with fear of falling and falls risk.[46] For example, sway lengths ≥400 mm have been associated with a 75% increase in the risk of falls in older adults.[47]

While balance impairments have been reported in people with long COVID and people with ME/CFS, these 2 patient groups have never been compared directly. This could be of interest as long COVID is a relatively new condition, and therefore it could be speculated that people with ME/CFS would have poorer postural control and physical capacity as they have been suffering from their post-viral illness longer, therefore experiencing the multi-systems disease progression and deconditioning for a longer time. To date, however, there have not been any studies that directly compare postural control and physical capacity in people with ME/CFS and people with long COVID in the same paper. Given the considerable overlap with long COVID and ME/CFS, we sought to examine postural sway and performance of physical capacity tests, compared with health controls. The Timed Up and Go test, the 5 Times Sit to Stand test, and the static stance test are widely reported in literature and frequently utilized to assess mobility, transitional skills, and balance, respectively.[26,48-50] In addition to performance outcomes of the Timed Up and Go test and the 5 Times Sit to Stand test, we sought to examine transitionary performance (eg, time from seating to standing, time from standing to seating, and turn velocity) during these tasks for a more nuanced and detailed insight into where performance decrements occurred. We also measured postural sway during a 30-s static standing balance test to identify individuals who did not meet thresholds indicative of physical impairment (both the Timed Up and Go and 5 Times Sit to Stand tests have thresholds for muscle weakness), but who may demonstrate excess postural sway, indicative of an increased fall risk or other comorbidity.[50,51]

The objective of this case-case-control study was to investigate the effects of long COVID and ME/CFS on 2 physical capacity tasks performance and postural sway during a 30-s static balance test. This experiment compared postural sway and performance of physical capacity tests between individuals with long COVID, individuals with ME/CFS, and age-matched healthy controls. We hypothesized that people with long COVID and ME/CFS would perform worse in the tests and would exhibit greater postural sway than healthy controls during a 30-s static balance test.

METHODS

Participants

Sixty-one participants (long COVID, n = 21; ME/CFS, n = 20; and healthy controls, n = 20, Table) were recruited for this study via social media advertisement using Facebook and Twitter platforms. Participants attended a one-off visit to the Cardiovascular Imaging laboratory at the University of the West of Scotland, Lanarkshire, between March 2022 and January 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 prior to study commencement. Descriptive statistics for participants are shown in the Table, and further described in the Results section.

Table Descriptive Data of Participants at Enrollment

Variable	Group	Mean ± SD
Age (years)	Long COVID (n = 21)	47 ± 10
	ME/CFS (n = 20)	50 ± 10
	Control (n = 20)	49 ± 10
Duration of illness	Long COVID (n = 21)	16 ± 6 mo
	ME/CFS (n = 20)	16 ± 11 y
	Control (n = 20)	N/A
Height (cm)	Long COVID (n = 21)	168 ± 10
	ME/CFS (n = 20)	169 ± 9
	Control (n = 20)	171 ± 9
Body mass (kg)	Long COVID (n = 21)	97 ± 23
	ME/CFS (n = 20)	87 ± 24
	Control (n = 20)	71 ± 15
BMI ($kg \cdot m^2$)	Long COVID (n = 21)	34 ± 6
	ME/CFS (n = 20)	31 ± 9
	Control (n = 20)	24 ± 4
Systolic blood pressure (mm Hg)	Long COVID (n = 21)	140 ± 19
	ME/CFS (n = 20)	102 ± 33
	Control (n = 20)	94 ± 40
Diastolic blood pressure (mm Hg)	Long COVID (n = 21)	95 ± 15
	ME/CFS (n = 20)	87 ± 12
	Control (n = 20)	77 ± 8
Resting heart rate (beats per minute)	Long COVID (n = 21)	80 ± 14
	ME/CFS (n = 20)	82 ± 19
	Control (n = 20)	65 ± 10

BMI = body mass index; ME/CFS = myalgic encephalomyelitis/chronic fatigue syndrome.

Stature was measured using a wall-mounted stadiometer (SECA, CE0123; Hamburg, Germany). Participants were required to remove their shoes and stand in the anatomical position keeping a straight back and ensuring their heels were in contact with the floor; stature was recorded in centimeters. Body mass of each participant was recorded using electronic scales (SECA 876). Participants wore minimal clothing (shorts and t-shirt, where possible), and body mass was recorded in kilograms. Body composition determination was conducted in accordance with the International Society for the Assessment of Kinanthropometry.[52] Participants' body mass indexes (BMIs) were then calculated (BMI = kg/m^2) from the body composition values. Resting blood pressure (BP) of participants was measured using an automated sphygmomanometer (OMRON Healthcare, Hoofddorp, Netherlands), in accordance with the International Society of Hypertension protocol. Participants were seated, and the BP cuff was secured on their left arm, a few centimeters above the elbow crease. The machine was then initialized, and the cuff inflated to 200 mm Hg and subsequently deflated to 0 mm Hg. This process was repeated 3 times and recorded. A mean of the 3 trials was used for analysis. A 1-minute rest period between readings was used, deemed optimal for BP accuracy.

Postural Sway Measurement

Participants were fitted with the 3 inertial measurement units (Opal, APDM Inc; Portland, Ore) to measure acceleration of the sacrum (at the level of L5), and both the left and right ankles; these units were placed according to the manufacturer's instructions. For the 30-s static balance test, an X was marked on the floor where participants stood, 2 meters from another X marked at approximately eye level on the wall. Participants were instructed to remain still and stand with their hands on their hips and feet shoulder width apart while fixating on the marked X on the wall for 30 s. The isoinertial measurement units measured amplitude, frequency, and jerkiness of postural sway in the lateral and frontal plane and the software (MobilityLab, APDM Inc) provided 32 postural sway parameters, which we collapsed into 13 parameters (where software provided overall, lateral, and frontal parameters, we included only overall).

For the Timed Up and Go test, a chair was placed against the wall at the end of the laboratory and a 3-meter distance from the chair along the floor was measured out using a tape measure (Chesterman, Rabon, Sheffield, United

Kingdom) and an X was clearly marked on the floor at the end of this distance. Participants began the trial in a seated position; the software sounded a tone to mark the beginning of the trial. When prompted by the tone, participants stood and walked straight ahead to the marked X, turned around, walked back to the chair, and sat down. Participants were instructed to walk at a comfortable and natural pace and to not use their hands to assist them when standing up or sitting back down. Also stressed to the participants was the importance of resting their back against the chair upon sitting back down for the lumbar isoinertial measurement units to determine timings. The software automatically detected standing, turning, and sitting (and thus, the overall duration).

For the 5 Times Sit to Stand test, participants were instructed to cross their hands over their chest to avoid use of their hands to rise from the chair. Participants rose from seated, and returned to seating, 5 times. The software automatically detected standing and sitting (and thus, the overall duration).

Statistical Analysis

All data were assessed for normal distribution and homogeneity of variance. To assess the differences in dependent variables, Welch's one-way analyses of variance (ANOVA) were performed, with Games-Howell post hoc tests performed where necessary. Data were analyzed using Jamovi (Version 2.3.21). Data are presented without subjective terminology and alpha levels are reported as exact *P* values, without dichotomous interpretation of "significant" or "non-significant", as advised by the American Statistical Association.[53] 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 for small, moderate, and large effects, respectively, were used for Cohen's *d*.[54] Figures were generated in GraphPad Prism (GraphPad Prism 8.4.3, GraphPad Software Inc., San Diego, Calif) and display grouped dot plots with mean and 95% confidence intervals, as recommended by Drummond and Vowler.[55,56] Figures also display pairwise comparisons in the form of Games-Howell post hoc *P* values, and Cohen's *d* values. Data are presented in text as mean ± SD.

RESULTS

Descriptive participant parameters are displayed in the Table. Pairwise differences between long COVID, ME/CFS, and controls for age and height were trivial to small ($P > .67$, $d < 0.31$). Long COVID participants were heavier than ME/CFS ($P = .272$, $d = 0.55$; medium effect) and controls ($P < .001$, $d = 2.10$; large effect). ME/CFS participants were heavier than controls ($P = .053$, $d = 0.80$; large effect). As a result of the differences in body mass, long COVID participants had a higher BMI than ME/CFS ($P = .406$, $d = 0.39$; small effect) and controls ($P < .001$, $d = 2.56$; large effect). ME/CFS participants were heavier than controls ($P = .003$, $d = 1.44$; large effect). Long COVID participants had higher diastolic BP than ME/CFS (p<0.001, d=1.41; large effect) and controls ($P < .001$, $d = 1.47$; large effect). The ME/CFS group had higher diastolic BP than controls ($P = .296$, $d = 0.22$; small effect). Systolic BP was not different between long COVID and ME/CFS ($P = .950$, $d = 0.09$; trivial effect), while controls had lower systolic BP than long COVID ($P = .093$, $d = 1.50$; large effect) and ME/CFS groups ($P = .050$, $d = 0.65$; medium effect). Resting heart rate was not different between long COVID and ME/CFS groups ($P = .970$, $d = 0.12$; trivial effect), while controls had lower resting heart rate than long COVID ($P < .001$, $d = 1.23$; large effect) and ME/CFS cohorts ($P = .005$, $d = 1.12$; medium effect).

Of the ME/CFS participants, 3 were in a wheelchair so unable to complete the 3 tests. Postural sway parameters derived from the 30-s static balance test are displayed in Figure 1. The ANOVA main effect of group was $P = .023$ for 95% ellipse axis 1 radius acceleration, $P < .001$ for 95% ellipse axis 2 radius acceleration, $P = .019$ for 95% ellipse rotation acceleration, $P = .003$ for 95% ellipse sway area acceleration, $P = .023$ for centroidal frequency, $P = .190$ for frequency dis-

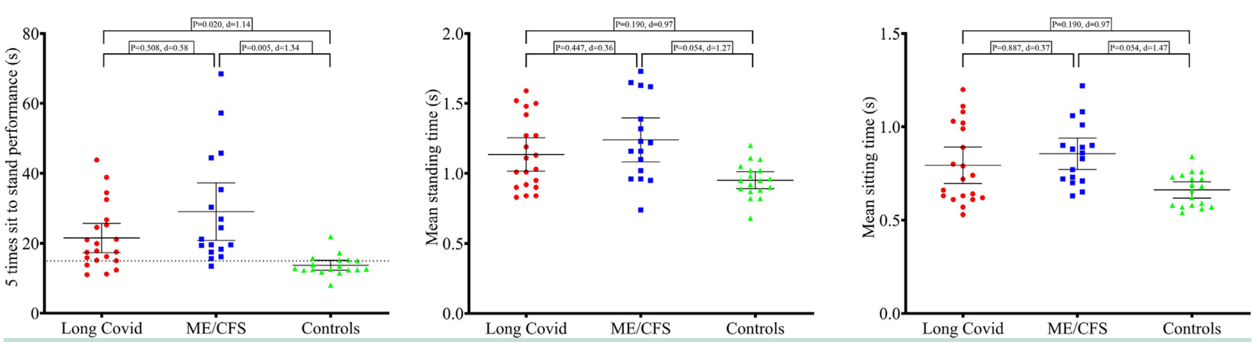

Figure 1 Postural sway parameters from people with long COVID (n = 21), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (n = 17), and controls (n = 19) during a 30-s static balance test. Data are presented as individual dot plots and means and 95% confidence intervals. RMS = root mean square.

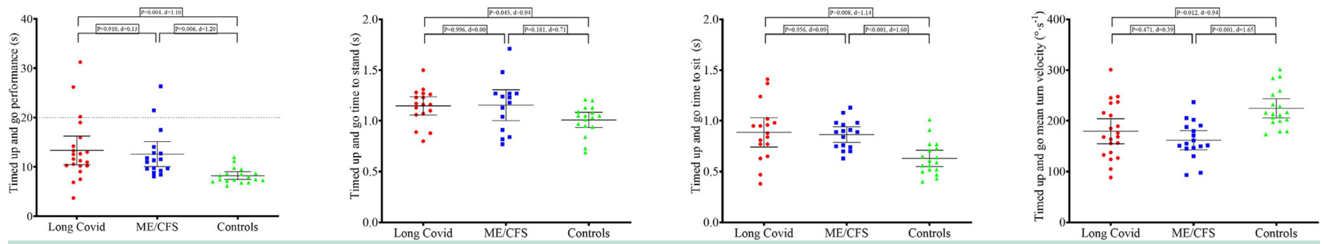

Figure 2 Parameters from people with long COVID (n = 21), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (n = 17), and controls (n = 19) during a Timed Up and Go test. Data are presented as individual dot plots and means and 95% confidence intervals. Additionally, the 20-s threshold for muscle weakness is indicated by the dashed line.

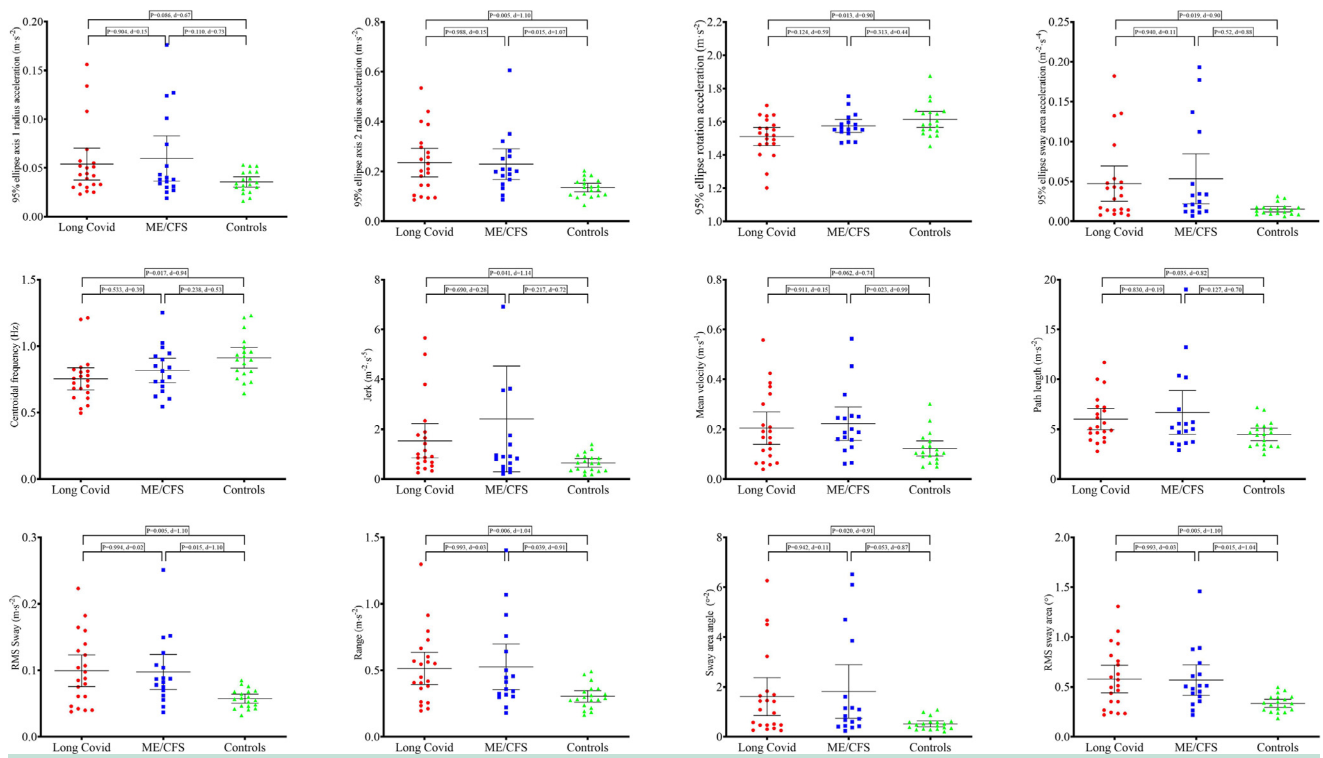

Figure 3 Parameters from people with long COVID (n = 21), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (n = 17), and controls (n = 19) during a 5 Times Sit to Stand test. Data are presented as individual dot plots and means and 95% confidence intervals. Additionally, the 15-s threshold for muscle weakness is indicated by the dashed line.

persion, $P = .018$ for jerk, $P = .008$ for mean velocity, $P = .016$ for path length, $P < .001$ for RMS sway, $P = .001$ for range, $P = .003$ for sway area angle, and $P < .001$ for RMS sway angle. As frequency dispersion main effect of group was $P = .190$, post hoc Games-Howell tests were not conducted, and the data are not visualized in Figure 1 for brevity.

Parameters derived from the Timed Up and Go test are displayed in Figure 2. The ANOVA main effect of group was $P < .001$, $P = .037$, $P < .001$, and $P < .001$ for total duration (ie, performance), time taken to stand, time taken to sit, and mean turn velocity, respectively.

Parameters derived from the 5 Times Sit to Stand test are displayed in Figure 3. The main effect of group from the ANOVA was $P < .001$ for all 3 parameters.

DISCUSSION

The purpose of this study was to compare postural sway and performance of physical capacity tests between people with long COVID, people with ME/CFS, and age-matched healthy controls. The main findings of the present investigation were that people with ME/CFS and people with long COVID were generally comparable for measures of postural sway during the 30-s static balance test. Similarly, their performances in the Timed Up and Go test and 5 Times Sit to Stand test were comparable. It is worth noting, however, that both these patient groups performed these tests more poorly than healthy controls. Additionally, and as represented by the individual dot plots, not only were mean values of the 2 patient groups poorer than controls, the spread was far larger, indicating that some participants were very impaired in terms of physical capacity. Thus, we accept our hypothesis that people with long COVID and ME/CFS would perform worse in the tests and exhibit greater postural sway than healthy controls during the examined tests.

The implications of these findings are that both people with long COVID and people with ME/CFS might be at greater risk of falling based on meta-analytical evidence.[57] Quijoux et al[57] reported that in 29 studies, retrospective classification of patients' fall status identified several parameters associated with future falls. In the present study, both long COVID and ME/CFS cohorts had worse values than healthy controls for path length, mean velocity, range, and sway area (parameters identified by Quijoux et al[57]), while having only trivial differences from each other. It may have seemed logical a priori that there would be some association between participants' static balance performance and the duration of their respective conditions. However, that was not the case; there were only trivial differences in balance measures despite large differences in duration of their conditions (mean duration for ME/CFS cohort was 16 years, vs 16 months for those with long COVID). Interpretation of these data is difficult given how little we know about long COVID and the dearth of any comparative data about the duration of ME/CFS and static balance. It may be that the data presented here represent basement effects, and longer durations of long COVID will see limited further deterioration. However, it is also possible that in a relatively short period, participants with long COVID have deteriorated to a similar degree as those with ME/CFS have over several years. If the rate of decline were to continue, it would seem inevitable that those with long COVID would be at increased risk of falls.

For the Timed Up and Go test, >20 s for 5 rises has been identified as a threshold for muscle weakness.[58,59] Although at the group level, mean Timed Up and Go values in long COVID and ME/CFS groups were less than the 20-s threshold used to identify for muscle weakness,[58,60] there were 5 individuals across both patient groups (3 long COVID and 2 ME/CFS; 14% of long COVID and 12% of ME/CFS) who did not achieve a time of <20 s, and are therefore at risk of muscle weakness, which has a large number of associated comorbidities.[58,61,62] Compared with the healthy control group, which contained no participants who failed to reach the 20-s threshold, this indicates that both people with ME/CFS and long COVID need support to adapt their occupational and habitual environments and schedules to accommodate their level of physical capacity. Alternatively, rehabilitation programs that target muscle strengthening could be of interest, however, people with ME/CFS and long COVID experience severe fatigue, so rehabilitation should be explored with extreme caution, and likely only in a subset of individuals. Our findings suggest that people with long COVID and ME/CFS have impaired physical capacity, which may contribute to their fatigue and disability. This will have significant impact upon physical capacity of people with long COVID. In addition to the obvious effects on the individual and family and friends of people with long COVID, this will result in significant economic consequences. Already, 2.5 million people are out of the labor force in the United Kingdom because of long-term sickness,[63] and this number could increase if disease progression continues beyond the 3 years since long COVID was coined. For the 5 Times Sit to Stand test, >15 s for 5 rises has been identified as a threshold for muscle weakness.[58,59] Concerningly, group means for both long COVID and ME/CFS exceeded this threshold, and 17 long COVID participants (81%) and 16 ME/CFS participants (94%) would be considered to have low strength according to the European Working Group on Sarcopenia in Older People. However, 3 controls (16%) also fell short of the 15-s threshold, calling into question the validity (especially the specificity) of the test or the threshold.

Limitations

This study is not without limitations, which we must acknowledge. First, the sample size was relatively small. We have attempted to overcome our limited sample size by including magnitude-based inferences and reporting exact α values, rather than relying on dichotomous "significant" and "non-significant". This was appropriate as, given that long COVID is a relatively new condition, meaning measures of central tendency and spread are rather unknown, particularly for postural sway parameters, a sample-size calculation was impossible. Second, findings may not be generalizable to the wider population of people with long COVID (or ME/CFS), particularly those who are unable to attend a laboratory (ie, those most severely affected). We are aware this is not entirely inclusive for people with long COVID and ME/CFS as, according to the National Institute for Health and Care Excellence, 25% of people with ME/CFS are bedbound or housebound, meaning that visiting a laboratory is impossible.[40] This was emphasized as 3 of our ME/CFS participants were in wheelchairs, so were unable to complete the postural sway test or physical capacity tests. Therefore, the magnitude of difference in physical capacity deficits presented herein likely underestimates the true effect due to the nature of recruitment bias. Finally, the study did not assess the impact of the impaired postural control and physical capacity on the quality of life of people with long COVID and ME/CFS.

CONCLUSION

In conclusion, findings of this study have important implications for the diagnosis and management of people with long COVID and ME/CFS. People with long COVID have physical capacity and postural sway similar to people with ME/CFS, despite having the post-viral illness for a mean of only 16 months rather than 16 years (as in the ME/CFS participants). This impaired postural control and physical capacity in people with long COVID may contribute to their fatigue and disability, and it is important to identify and address these issues in order to improve their quality of life. Furthermore, as we are at the start of the long COVID pandemic, there is a real concern that these physical capacity decrements may worsen over the next few years, having serious implications for the individual, their familial and social network, and worldwide economies. Patient groups often report a tension between their view that their physical symptoms are their primary concern and clinical services, which may focus on psychosocial factors. The present study's findings support the now overwhelming evidence that ME/CFS and long COVID have real, physiological symptoms that impact health and well-being and need to be directly addressed. Future research should focus on identifying the mechanisms underlying long COVID and ME/CFS and on developing interventions to improve outcomes.

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