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Post-Traumatic Stress Disorder and Complex Post-Traumatic Stress Disorder in people with long COVID, ME/CFS, and controls

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COVID and ME/CFS

Abstract

Background

Prevalences of Post-Traumatic Stress Disorder (PTSD) and Complex Post-Traumatic Stress Disorder (CPTSD) have not previously been compared between individuals with long COVID and individuals with Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS), and healthy age-matched controls. For these reasons, this study aimed to determine the prevalence of PTSD and CPTSD in individuals with long COVID (n=21) and ME/CFS (n=20) and age-matched controls (n=20).

Methods

A case-case-control approach was employed, participants completed the International Trauma Questionnaire (ITQ), a self-report measure of the International Classification of Diseases (ICD-11) of PTSD and CPTSD consisting of 18 items. Scores were calculated for each PTSD and Disturbances in Self-Organization (DSO) symptom cluster and summed to produce PTSD and DSO scores. PTSD was diagnosed if the criteria for PTSD were met but not DSO, and CPTSD was diagnosed if the criteria for PTSD and DSO were met. Moreover, each cluster of PTSD and DSO were compared among individuals with long COVID, ME/CFS and healthy controls.

Results

Individuals with long COVID (PTSD= 5%, CPTSD= 33%) had more prevalence of PTSD and CPTSD than individuals with ME/CFS (PTSD= 0%, CPTSD= 20%) and healthy controls (PTSD= 0%, CPTSD= 0%). PTSD and CPTSD prevalence was greater in individuals with long COVID and ME/CFS than controls. Individuals with long COVID had greater values controls for all PTSD values. Moreover, individuals with long COVID had greater values than controls for all DSO values. Individuals with ME/CFS had greater values than controls for all DSO values. Both long COVID and ME/CFS groups differed in overall symptom scores compared to controls.

Conclusion

Findings of this study demonstrated that individuals with long COVID generally had more cases of PTSD and CPTSD than individuals with ME/CFS and healthy controls.

Key words

Myalgic Encephalomyelitis, Chronic Fatigue Syndrome, long COVID, post-traumatic stress disorder, complex post-traumatic stress disorder, trauma

Introduction

The COVID-19 pandemic had a profound impact on global public health [1–4]. An emerging and dynamic finding is the presence of symptoms such as anxiety, depression, insomnia and trauma related symptoms seen in COVID-19 survivors (individuals who tested positive for coronavirus and/or who were later confirmed to have had the virus by testing positive for antibodies), as documented in numerous studies [5–8]. The long-term course of the symptoms such as anxiety, depression, insomnia and trauma related symptoms in COVID-19 survivors reveals a trajectory characterised by exacerbation over time, particularly in the case of conditions associated with post-traumatic stress disorder (PTSD) [6]. Individuals who have faced a fear of survival remain vulnerable to post-traumatic stress symptoms (PTSS), and hospitalisation during COVID-19 is a well-recognised risk factor for PTSD[9–12]. Several studies have documented a rapid onset of severe PTSS in COVID-19 survivors following hospital discharge[10,13–16] . Mazza et al. [10] documented the rapid onset of severe PTSS in COVID-19 survivors, typically within one month following hospital discharge. Matalon et al.[13] revealed a direct association between higher levels of anxiety and depression during the first week of hospitalisation, social isolation, and prolonged hospital stays with higher post-traumatic stress symptoms one month after discharge. Tu et al. [14] reported the persistence of PTSS in COVID-19 survivors from Wuhan, extending to three- and six-months post-discharge. Neuroimaging studies indicate larger gray matter volumes and increased functional activities in the bilateral hippocampus and amygdala of COVID-19 survivors, two regions associated with the pathophysiology of PTSS [15]. Cao and colleagues [16] demonstrated that one year on after COVID-19, the prevalence of possible post-traumatic stress disorder was 12.4% and this finding seemed to match up with socio-demographic factors.

Only one in three people fully recover from COVID-19 a year after hospital discharge [17]. Individuals that have persistent symptoms lasting over 12 weeks after the acute phase of the COVID-19 infection are known to suffer from long COVID. Long COVID share similarities and several overlapping symptoms with another condition known as Myalgic Encephalomyelitis (ME), Chronic Fatigue Syndrome (CFS), and/or ME/CFS [18,19]. Individuals with long COVID are reported to experience new and worsening mental health symptoms. Most frequently reported were depression, anxiety, PTSS, and insomnia [20]. Moreover, it has been revealed that there is a link between childhood trauma exposure and an increased risk of long COVID, possibly attributed to immune responses, peripheral dysfunction, and central sensitisation[21]. Nishimi et al.[22] reported that higher psychological resilience to trauma reduced the likelihood of COVID-19 infection but was not associated with COVID-19 severity or long COVID, but only associated with lower likelihood of COVID-19 infection over time. In terms of the association between PTSD and Chronic Fatigue Syndrome (CFS), Simani et al.[23] found no significant association between PTSD and increased risk of CFS in COVID-19 patients.

Taken together, past research suggests a link between PTSS and COVID-19 survivors especially the hospitalised cases, and one year on after COVID-19, the prevalence of possible post-traumatic stress disorder is demonstrated to be about 12.4%[10,13–16]. Moreover, past research suggests a link between long COVID and PTSS, and childhood trauma exposure and increased long COVID risk[20,21]. Given that most hospitalised COVID-19 survivors do not fully recover from COVID-19 and develop long COVID [17,24], we sought to examine the prevalence of post-traumatic stress disorder (PTSD) and complex post-traumatic stress disorder (CPTSD) in individuals with long COVID. Furthermore, given the considerable overlap between long COVID and ME/CFS, we sought to examine prevalence of PTSD and CPTSD in individuals with ME/CFS. For that reason, the objective of this case-control study was to investigate the prevalence of PTSD and CPTSD in individuals with long COVID, individuals with ME/CFS and healthy age-matched controls. We hypothesised that individuals with long COVID would display higher prevalence and cluster scores of PTSD and CPTSD compared to the individuals with ME/CFS and age-matched healthy controls.

Methods

Participants

Following institutional ethics approval, sixty-one participants; 21 individuals with long COVID (aged M= 47 years, SD=10 years, duration of illness; M= 16 years, SD=6 months), 20 individuals with ME/CFS (aged M=50 years, SD=10 years, duration of illness; M=16 years, SD=11 years) and 20 healthy controls (aged M=49 years, SD=10 years, and no known illness) were recruited via social media (e.g. Twitter/X and Facebook/Meta) and attended the University of the West of Scotland Lanarkshire campus laboratories once between March 2022 and January 2023. This study was completed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to study involvement.

Materials and Apparatus

Participants completed the English version of the ITQ, this 18 question self-report measure that focuses on core features of PTSD and CPTSD consistent with ICD-11. The 18-item ITQ has six PTSD items, six DSO items and three functional impairment items related to each symptom cluster.

The first section of the 18-item ITQ is dedicated to three PTSD symptom clusters (P.1-P.6); re-experiencing of the trauma (P1-P.2), avoidance of internal or external trauma reminders (P.3-P.4), and a sense of current threat (P.5-P.6). These are measured by two items each. In this section, respondents reported how much they have been bothered by the symptoms in the past month. In the three

functional impairment items related to PTSD (P.7-P.9), respondents reported how the above problems affected their relationship or social life, work or ability to work, and other important part of their life such as parenting or school or work etc.

The second section consists of three main symptom clusters of DSO (C.1-C.6; affective dysregulation (C.1-C.2), negative self-concept (C.3-C.4) and disturbances in relationships (C.5-C.6). In the three functional impairment items (C.7-C.9), respondents reported how they typically felt about their relationships or social life, if work or ability to work had been affected, and how this affected other important parts of their lives such as parenting or school or work or other important activities.

All items are answered on a five-point Likert scale, ranging from "not at all" (scored 0) to "extremely" (scored 4). Scores were calculated for each PTSD and DSO symptom cluster and summed to produce PTSD and DSO scores. PTSD was diagnosed if the criteria for PTSD were met but not DSO, and CPTSD was diagnosed if the criteria for PTSD and DSO were met. Criteria for PTSD was met if one of the two symptoms from the symptom clusters and at least one indicator of functional impairment associated with these symptoms were scored two or above. Criteria for CPTSD was met if one of the two symptoms from each of the three PTSD symptom clusters and one of the two symptoms for each of the three DSO, and at least one indicator of functional impairment related to PTSD, and one indicator of functional impairment related to the DSO symptoms were scored two or above. Endorsement of a symptom or functional impairment item was therefore defined as a score ≥ 2. Thus, a person can be classified as having a score commensurate with PTSD *or* CPTSD, but not both.

PTSD

If P1 or P2 ≥ 2

If P3 or P4 ≥ 2

If P5 or P6 ≥ 2

AND

At least one of P7, P8 or P9 ≥ 2

CPTSD

If C1 or C2 ≥ 2

If C3 or C4 ≥ 2

If C5 or C6 ≥ 2

AND

At least one of C7, C8 or C9 ≥ 2

PTSD is diagnosed if the criteria for PTSD are met but not the criteria for DSO. CPTSD is diagnosed if the criteria for PTSD are met and the criteria for DSO are met.

Procedure

Participants were seated in front of a table that had one information sheet, a consent form, a demographic sheet and the ITQ. Participants were instructed to read the information sheet, complete the consent form, complete the demographic form, and then complete the ITQ. Participants were informed their answers were anonymous.

Statistical Analysis

All data were assessed for normal distribution and homogeneity of variance. To assess the differences dependent variables, Welch's one-way analyses of variance (ANOVA) were performed with Games-Howell post-hoc tests performed where necessary. The $\chi 2$ test was performed to determine whether a difference in prevalence of PTSD, and CPTSD existed between the three groups existed. Post-hoc pairwise Fisher's exact test tested for a difference in affected (PTSD or CPTSD) and not between groups. Data were analysed 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 [25]. Effect size for paired comparisons was conducted using Cohen's *d* whereby the difference in means between two samples was divided by the pooled standard deviation (SD). Thresholds of 0.2, 0.5, 0.8, and 1.2 for small, moderate, large, and very large effects were used for Cohen's *d* [26]. Figures were generated in GraphPad Prism (GraphPad Prism 8.4.3, GraphPad Software Inc., San Diego, CA, USA) and display grouped dot plots with mean and 95% confidence intervals (CIs) as recommended by Drummond and Vowler [27,28]. 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 Statistics and Prevalence

Prevalence of PTSD and CPTSD in the three groups are displayed in table 1. The $\chi 2$ test resulted in a difference in prevalence of PTSD, and CPTSD between the three groups (p=.038). Fisher's exact test identified no difference in prevalence of PTSD *or* CPTSD between the long-COVID and ME/CFS groups (p=.3058). Fisher's exact test identified a greater prevalence of PTSD *or* CPTSD between the long-COVID and control groups (p=.003). Fisher's exact test identified no difference in prevalence of PTSD *or* CPTSD between the ME/CFS and control groups (p=.106).

Table 1. Prevalence of PTSD and CTPSD in people with long COVID, people with ME/CFS, and controls.

	Prevalence of each condition; n (%)		
	Long COVID (n=21)	ME/CFS (n=20)	Controls (n=20)
PTSD	1 (5%)	0 (0%)	0 (0%)
CPTSD	7 (33%)	4 (20%)	0 (0%)
Neither PTSD nor CPTSD	13 (62%)	16 (80%)	20 (100%)

Reasons for the Experience

For people with long COVID, six mentioned the experience of COVID (29%), five mentioned long COVID (24%), three mentioned health (14%), two mentioned fatigue (9%), two mentioned pain (9%), one mentioned brain fog (5%), one mentioned childbirth (5%), and one mentioned no reason for their experience (5%). For experience occurrence time, ten mentioned 1 to 5 years ago (48%), eight mentioned 6 to 12 months ago (38%), two mentioned less than six months ago (9%), and one did not specify time (5%). Among the seven that met the criteria for CPTSD, three mentioned long COVID (43%), two mentioned COVID (29%), one mentioned health (14%), and one mentioned pain (14%) as their reason behind their experience. Among these, two mentioned the experience of long COVID occurred 1 to 5 years ago (29%) and one mentioned it occurred 6 to 12 months ago (14%). Two mentioned the experience of COVID occurred 1 to 5 years ago (29%), one mentioned experience of health occurred 6 to 12 months ago (14%), and one mentioned experience of pain occurred 6 to 12 months ago (14%). One person that met criteria for PTSD, mentioned health as their reason behind their experience, and mentioned it occurred 6 to 12 months ago.

COVID and ME/CFS

For people with ME/CFS, ten mentioned ME/CFS (50%), two mentioned no reason for their experience (10%), two mentioned health (10%), one mentioned fatigue (5%), one mentioned illness (5%), one mentioned surgery (5%), one mentioned upbringing (5%), one mentioned work stress (5%) and one mentioned work dismissal (5%) as a reason behind their experience. For experience occurrence time, six mentioned it occurred 10 to 20 years ago (30%), five mentioned it occurred 5 to 10 years ago (25%), three mentioned it occurred more than 20 years ago (15%), two mentioned 1 to 5 years ago (10%), two mentioned no time (10%), one mentioned 6 to 12 months ago (5%) and one mentioned less than six months ago (5%).Among the four that met the criteria for CPTSD, three mentioned ME/CFS (75%), and one mentioned surgery (25%) as their reason behind their experience. Among these, two mentioned their experience of ME/CFS occurred more than 20 years ago (50%), and one mentioned it occurred 1 to 5 years ago (25%). One mentioned that their experience of surgery occurred 5 to 10 years ago (25%).

Among the 20 healthy control participants no one met the criteria for CPSTD or PTSD. For the reason behind the experience, seven mentioned health (35%), three mentioned no reason (15%), three mentioned bereavement (15%), two mentioned flying (10%), one mentioned cancer diagnosis of family member (5%), one mentioned injury (5%), one mentioned giving birth (5%), one mentioned illness of family member (5%), and one mentioned premature birth of family member (5%). For experience occurrence time, five mentioned it occurred 1 to 5 years ago (25%), five mentioned it occurred 5 to 10 years ago (25%), five did not mention a time frame (25%), three mentioned 10 to 20 years ago (15%), one mentioned less than 6 months ago (5%), and one mentioned more than 20 years ago (5%).

PTSD and DSO

PTSD

The was an effect of group for re-experiencing in the here and now, avoidance, and sense of current threat, overall PTSD score, and PTSD impairment ($F(2,58)=3.71$, $p=.03$; $F(2,58)=6.77$, $p<.01$, $F(2,58)=6.74$, $p<.01$; $F(2,58)=6.61$, $p<.01$; and $F(2,58)=17.87$, $p<.001$ respectively). Pairwise comparisons (Games-Howell post-hoc test *p* values and *Cohen's d* values) are presented in figure 1.

COVID and ME/CFS

*****INSERT FIGURE 1 ABOUT HERE******

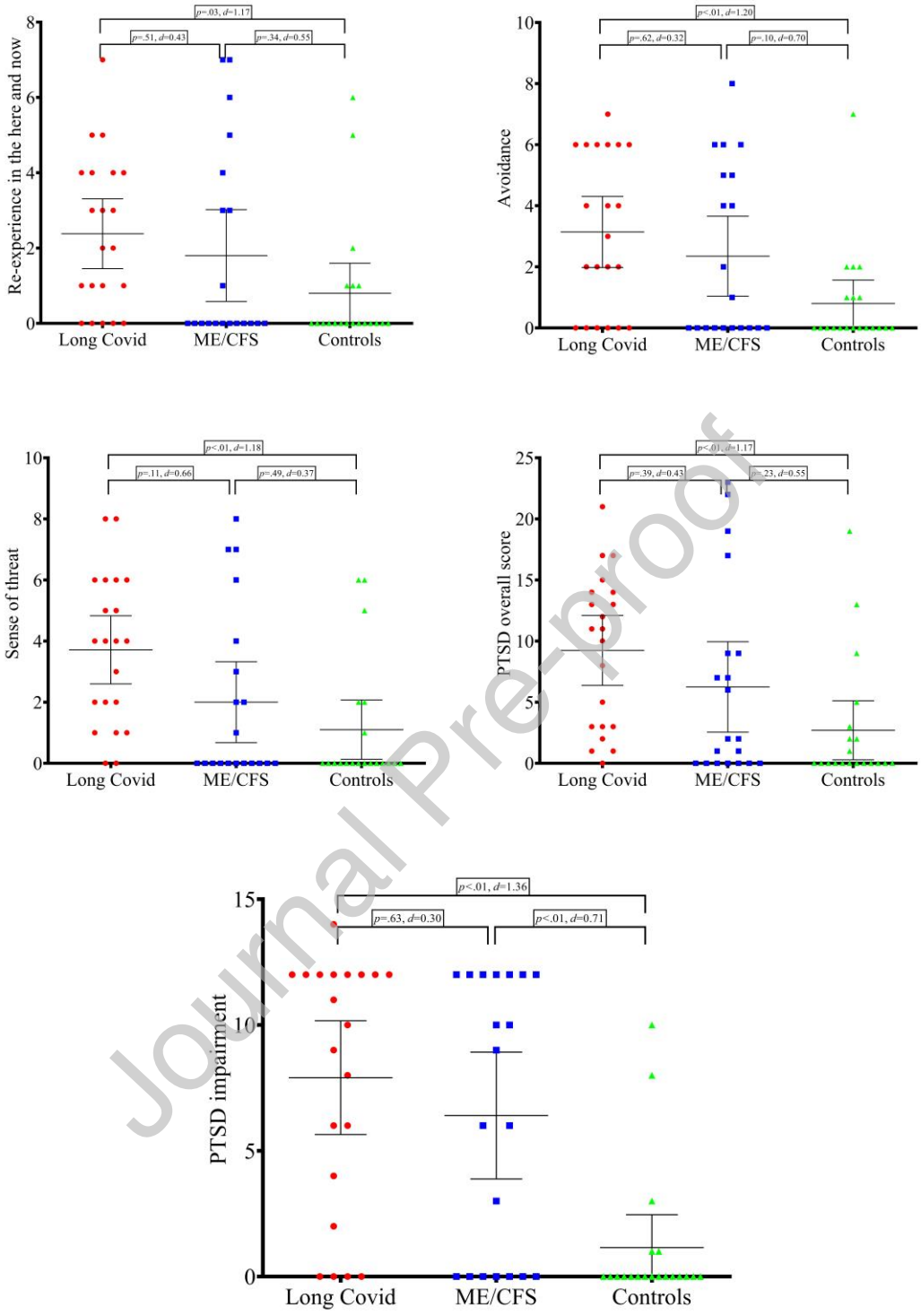

Figure 1. International Trauma Questionnaire (ITQ) results for the Post Traumatic Stress Disorder (PTSD) items in people with Long-COVID (n=21), ME/CFS (n=20), and controls (n=20). Data are presented as individual dot plots and means and 95% confidence intervals. *p* values are from Games-Howell post-hoc tests and *d* values are Cohen's *d*.

DSO

The was an effect of group for affective dysregulation, negative self-concept, disturbances in relationship, overall DSO score, and DSO impairment *(F*(2,58)=10.99, *p<.001; F*(2,58)=15.60, *p<.001*; *F*(2,58)=16.77, *p<.001*; *F*(2,58)=15.20, *p<.001*; and *F*(2, 58)=15.36, *p*<.001 respectively). Pairwise comparisons (Games-Howell post-hoc test *p* values and Cohen's *d* values) are presented in figure 2.

COVID and ME/CFS

*****INSERT FIGURE 2 ABOUT HERE******

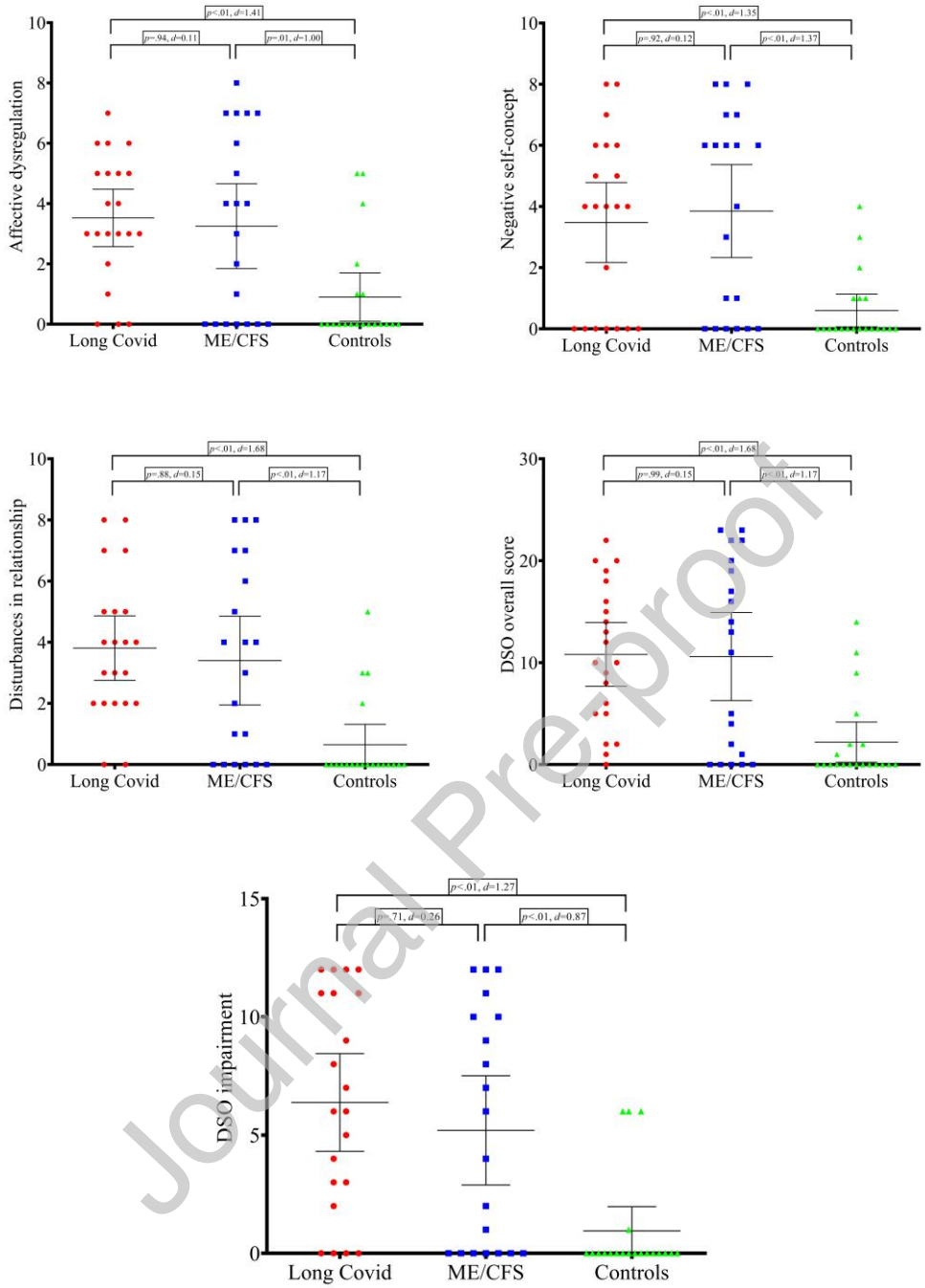

Figure 2. International Trauma Questionnaire (ITQ) results for the Disturbances in Self-Organization (DSO) items in people with Long-COVID (n=21), ME/CFS (n=20), and controls (n=20). Data are presented as individual dot plots and means and 95% confidence intervals. *p* values are from Games-Howell post-hoc tests and d values are Cohen's *d*.

Overall International Questionnaire (ITQ) Score

There was a main effect of group for overall ITQ score for CPSTD *(F*(2,58)=17.00, *p<.001)*. Individuals in the long COVID group (M=34.33, SD=19.30) scored higher (*p*<.001) than the healthy controls (M=7.00, SD=12.20). Individuals in the ME/CFS group (M=28.45, SD=24.90) scored higher (*p*=.01) than the healthy controls (M=7.00, SD=12.20).

Discussion

The purpose of this study was to examine the prevalence of PTSD and CPSTD, and cluster of PTSD and DSO in people with long COVID, people with ME/CFS, and age-matched healthy controls. The main findings of the present investigation were that there was a difference in prevalence between individuals with long COVID, individuals with ME/CFS and age-matched healthy controls. PTSD and CPTSD prevalence were greater in individuals with long COVID and individuals with ME/CFS compared to age-matched healthy controls. Individuals with long COVID had greater raw values than age-matched healthy controls for all PTSD values. Moreover, individuals with long COVID had greater raw values than age-matched healthy controls for all DSO values. Individuals with ME/CFS had greater values than age-matched healthy controls for all DSO values. Both long COVID and ME/CFS groups had higher symptom scores compared to controls.

The spread of data within each group was large, evidenced by the individual dot plots and large confidence intervals, suggesting considerable within-group heterogeneity. However, our findings were partially in line with our hypothesis of higher prevalence of PTSD and CPTSD, and cluster scores of PTSD and DSO in individuals with long COVID compared to individuals with ME/CFS and controls. This difference was not as apparent between individuals with long COVID and ME/CFS, although there was a very large difference between individuals with long COVID and control participants, and a moderate difference between individuals with ME/CFS and control participants, for PTSD impairment. In the DSO cluster, the difference between long COVID and control participants was very large, and the difference between the ME/CFS and control group was large.

Individuals with long COVID reported experience occurrence time to be fewer in years compared to the individuals with ME/CFS. For example, ten mentioned 1 to 5 years ago (48%), eight mentioned 6 to 12 months ago (38%), two mentioned less than six months ago (9%), and one did not specify time (5%) in individuals with long COVID. Whereas, six mentioned it occurred 10 to 20 years ago (30%), five mentioned it occurred 5 to 10 years ago (25%), three mentioned it occurred more than 20 years ago (15%), two mentioned 1 to 5 years ago (10%), two mentioned no time (10%), one mentioned 6 to 12 months ago (5%) and one mentioned less than six months ago (5%) in individuals with ME/CFS. This suggests individuals with ME/CFS have been suffering from the post-viral symptoms longer than individuals with long COVID and may explain the larger differences from controls in the long COVID group compared to the ME/CFS group. There might be other contextual differences among

these groups in terms of acceptance of condition, letting go of past events, and dealing better with current symptoms due to greater experience of similar symptoms over time etc. Individuals with long COVID lived through the stressors of a pandemic whilst dealing with their own symptoms and COVID survivors may have been hospitalised and seen passing of lives in hospitals.

Past research suggests individuals that have faced a fear of survival remain vulnerable to PTSS and hospitalisation is a well- recognised risk factor for PTSD, with a rapid onset of severe PTSS within one month following hospital discharge, this has been reported to extend to three and six months post-discharge[6,9–12,14]. The longest duration of post-discharge that has been examined is one year on after COVID-19, PTSD was reported to be 12.4% and there was an interplay with socio-demographic factors[16]. The current study was conducted two years after the COVID-19 pandemic started, but our entire sample were not hospitalised prior and have developed long COVID. Past research on long COVID and PTSS suggest new and worsening mental health symptoms among Long COVID individuals, most frequently reported were post-traumatic stress symptoms (PTSS) among few other such as depression and anxiety etc[20]. However, this study does not explain how these mental health symptoms change over time in individuals with long COVID, thus a study examining these changes could be beneficial in creating awareness around mental health issues within the long COVID population to better support them.

Limitations

This study presents a few limitations which we must acknowledge. Firstly, the sample size was relatively small, and therefore we encourage readers to consider effect sizes in addition to *p* values to contextualise findings. Secondly, 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 (i.e., 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. Therefore, the magnitude of differences in psychological well-being presented herein likely underestimates the true effect due to the nature of recruitment bias. Finally, the study did not assess hospitalisation or the impact of hospitalisation on mental health.

Conclusion

In conclusion, findings of this study demonstrate that people with long COVID had greater prevalence of PTSD and CPTSD than people with ME/CFS and controls. Individuals with long COVID demonstrate higher scores in PTSD and DSO clusters compared to controls, but no differences at the

$p<0.05$ level existed for PTSD and DSO clusters between the long COVID and the ME/CFS groups. Both long COVID and ME/CFS groups differed in overall symptom scores compared to control group, but magnitudes were heterogenous. Future research should focus on examining this relationship with a larger sample, and on developing mental health support strategies to aid individuals suffering with a post-viral condition.

Authorship contributions according to the CRediT taxonomy

Conceptualisation: N.E.M.S-H., L.D.H, E.C.B., M.M., and N.F.S.; methodology, N.E.M.S-H., L.D.H, M.M., and N.F.S.; software, N.E.M.S-H., L.D.H, E.C.B., M.M., and N.F.S.; validation, N.E.M.S-H., L.D.H, E.C.B., M.M., and N.F.S.; formal analysis, N.E.M.S-H.; investigation, N.E.M.S-H., L.D.H, M.M., E.C.B., and N.F.S.; resources, L.D.H, and N.F.S.; data curation, N.E.M.S-H., L.D.H, E.C.B., and M.M.; writing—original draft preparation, N.E.M.S-H.; writing—review and editing, N.E.M.S-H., L.D.H, M.M., E.C.B., and N.F.S.; visualisation, N.E.M.S-H., and L.D.H.; supervision, N.F.S; project administration, N.E.M.S-H., L.D.H, M.M., E.C.B., and N.F.S.; funding acquisition, L.D.H, and N.F.S. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest statement

The submitted work was not carried out in the presence of any personal, professional, or financial relationships that could potentially be construed as a conflict of interest.

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COVID and ME/CFS

Clinical Significance

- People with long COVID and ME/CFS exhibit higher prevalence of Post-Traumatic Stress Disorder (PTSD) and Complex Post-Traumatic Stress Disorder (CPTSD) than controls.
- Prevalence of PTSD and CPTSD puts these groups at greater risk of employment and activities of daily living challenges.
- As a result of the above, rehabilitation programmes should be implemented, or accommodations for activities of daily living and employment should be made for people with long COVID and ME/CFS.

Conflicts of Interest

I am writing this Declaration of Competing Interest Statement on behalf of all co-authors of the manuscript titled "Prevalence of Post-Traumatic Stress Disorder (PTSD) and Complex Post-Traumatic Stress Disorder (CPTSD) in people with long COVID, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), and controls: A case-case-control study".

The authors whose names are listed immediately below certify that they have NO declarations of competing interest. All co-authors have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.