The relationship between stress and mental outcomes persisting beyond the acute infection period of COVID-19

Madeleine Jane Ashton

Department of Psychology, University of Cape Town

Professor Mark Solms, Dr Donné Minné, and Altay Yüce Turan

December 23, 2021

Abstract word count: 239 words

Main body word count: 7,987 words

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Abstract

Persistent poor mental outcomes are reported as part of the post-viral syndrome, long COVID, and as part of a stress response to the COVID-19 pandemic environment. These poor mental outcomes are broadly reported as symptoms of anxiety, depression, and fatigue. It is possible that these may be resulting from a stress response to the pandemic as stress has been identified to be strongly implicated in the aetiology of these symptoms. As this stress is common to both post-COVID and non-COVID persons, it is possible that reports of these mental outcomes between these two groups of people could be similar. To characterize long COVID, there is increasing need to distinguish these mental outcomes as COVID-19 sequelae rather than merely part of a stress response to the COVID-19 pandemic. The present study examined anxiety, depression, and fatigue in relation to perceived stress in a sample of 72 South African adults using self-report psychometric measures administered through an online survey. Within this sample, 57 were identified as likely long COVID participants and 15 as non-COVID participants. Poor mental outcomes were consistently reported with greater severity by post-COVID participants identified as likely to be experiencing long COVID than non-COVID participants. This indicates that mental poor mental outcomes are being reported differently by likely long COVID participants and non-COVID participants. No significant relationships, however, were found between stress and the mental outcomes reported as part of long COVID for likely long COVID participants.

Keywords: long COVID; COVID-19; perceived stress; fatigue; depression; anxiety; pandemic; post-viral syndrome; post-COVID mental outcomes.

The relationship between stress and mental outcomes persisting beyond the acute infection period of COVID-19

The coronavirus 19 (COVID-19) pandemic has contributed to poor mental outcomes across the population (Gallagher et al., 2020; Molodynski et al., 2021). These are frequently being reported by post-COVID patients as part of the post-viral syndrome, long COVID, but they are also being reported as part of a broad stress response to the COVID-19 pandemic environment by both post-COVID and non-COVID persons (Ettman et al., 2020; Hyland et al., 2020; Nalbandian et al., 2021; Shevlin et al., 2020). Specifically, poor mental outcomes are being reported in relation to anxiety, depression, and fatigue (Gaber, 2021; Huang et al., 2021; Kingstone et al, 2020).

Long COVID refers to symptoms that persist beyond the four-week acute phase of a COVID-19 infection (Ladds et al., 2020; Nalbandian et al., 2021; Taribagil et al., 2021). Symptoms of this post-viral syndrome have been reported to manifest both physiologically and mentally. Mental outcomes of long COVID are predominantly being reported in terms of symptoms related to anxiety, depression, and fatigue (Gaber, 2021; Graham et al., 2021; Ladds et al., 2020; Mendelson et al., 2020). However, further than these reports, the literature is unable to provide a precise characterization of the mental outcomes of long COVID (Kingstone et al, 2020; Wilson et al, 2020).

Contributing to the challenge of characterizing the mental aspects of long COVID is that not all people who become infected with COVID-19 experience the post-viral syndrome. Reports of poor post-COVID mental outcomes may subsequently not all be related to viral sequelae and may rather be arising as part of a response to the pandemic environment. This challenge is compounded as no clear diagnostic criteria for long COVID has yet been established. This means that the post-viral syndrome remains difficult to definitively diagnose.

For the purposes of this research, post-COVID persons identified as likely to be classified as long COVID patients according to the current understanding of the post-viral syndrome within the literature are referred to as likely long COVID (LLC) participants. This is because without definitive diagnostic criteria for long COVID, it is important to communicate a degree of uncertainty in how participants are classified.

A growing body of evidence indicates that the COVID-19 virus is both triggering and worsening mental outcomes in post-COVID (specifically LLC) patients following the acute phase of infection (Nalbandian et al., 2021; Proal & van Elzakker, 2021; van Eijk et al., 2021). This trend is in accordance with a wide body of literature which establishes that viral sequelae have the potential to cause a range of psychological and physiological symptoms after the acute infection period (Hart, 1998; Capuron & Dantzer, 2003). This suggests that there are differences in how mental outcomes are being reported by LLC persons and non-COVID persons, however, uncertainties remain surrounding where these differences lie. These symptomatic differences are important to understand and to validate as part of a post-viral syndrome especially given that complaints of persistent symptoms following a viral infection have historically been dismissed as displays of patient hysteria (David et al., 1998).

It is suggested that persistent symptoms following a COVID-19 infection may broadly relate to symptoms of "sickness behaviour". Sickness behaviour is understood to be a physiological attempt to conserve energy through behavioural adaptations which allow for greater energy to be channeled to the metabolic and physical defenses against an infection (Aubert, 1999; Hart, 1998). It is associated with increased cytokine activity in response to a viral infection beyond the acute viral infection period (Sanders, 2010). Symptoms include lethargy, a depressed mood, anorexia, and decreased social activity (Andreasson et al., 2016; Capuron & Dantzer, 2003; Dantzer et al., 2001). It is subsequently suggested that mental

outcomes associated with long COVID may be more related to sickness behaviour symptoms than for non-COVID persons.

Although there is evidence to suggest that viral sequelae may be contributing to a unique display of mental outcomes following a viral infection, debate continues as to whether these mental outcomes might be better understood as part of a physiological and psychological stress response to the pandemic environment. Much of this debate stems from evidence that the COVID-19 pandemic has resulted in higher levels of negatively perceived stress across populations internationally (Ettman et al., 2020; Hyland et al., 2020; Sher, 2021; Shevlin et al., 2020).

Social isolation and social distancing have been encouraged, and at times enforced, to combat the spread of the virus but they have also been found to profoundly impact the mental health of the population by intensifying feelings of loneliness and seclusion (Carvalho et al., 2020; Gruber et al., 2020; Troyer et al., 2020; Wang et al., 2020). The social and economic disruption caused by the pandemic have also demanded rapid (and often stressful) adjustments to how people live and work (Carvalho et al., 2020; Troyer et al., 2020). Further, with COVID-19 being one of the leading causes of death in 2020, the psychological impact of grief has both contributed to and worsened mental outcomes across the population (Gallagher et al., 2020; Wallace et al., 2020).

The literature indicates that environmental factors such as those discussed above can trigger a physiological stress response involving the coordination and regulation of the hypothalamic pituitary adrenal axis (HPA-axis), and subsequently neuroinflammation (Bilotta et al., 2018; Romero, 2004; Tapp et al., 2019). Through the HPA-axis, the precise mechanism that gives rise to neuroinflammation has been suggested to be related to cortisol as well as to pro-inflammatory cytokine activity (Chen et al., 2017; Silverman & Sternberg, 2012). Symptoms of anxiety, depression, and fatigue are frequently reported in relation to the

activation of these mechanisms and as part of a physiological stress response (Choi et al., 2020; Furtado & Katzman, 2015; Silverman et al., 2005; Troubat et al., 2021; Varghese & Brown, 2001). As an example, both Major Depressive Disorder and Generalized Anxiety Disorder, have been linked to higher levels of circulating proinflammatory cytokines (Simon et al., 2008; Tang et al., 2018; Young et al., 2014).

A physiological stress response to the pandemic environment may be contributing to similarities in mental outcomes being reported by both LLC and non-COVID persons. This is because environmental stressors (e.g., increased social isolation), as well as the mental complaints associated with a sustained physiological stress response (e.g., increased worry, low mood, and fatigue) have been experienced and reported both by those who have been infected with COVID-19 and by those who have not (Hyland et al., 2020; Shevlin et al., 2020). This suggests that both groups of people are vulnerable to prolonged elevations in the physiological stress response, heightened levels of circulating cytokines and subsequently, to similar poor mental outcomes (Tapp et al., 2019).

However, levels of circulating cytokines have been suggested to be particularly high for post-COVID persons. Enduring post-viral symptoms have been theorized to result from an exaggerated immune response, a “cytokine storm”, which in turn can cause and exacerbate neuroinflammation (Kamal et al., 2020; Ladds et al., 2020; Rudroff et al., 2020; Versace et al., 2021). This theory has been challenged by conflicting findings which indicate an unclear relationship between COVID-19 infection severity and persistent post-viral outcomes (Kingstone et al., 2020; Townsend et al., 2020). As stress has been found to be able to trigger and worsen neuroinflammation (Bilotta et al., 2018; Romero, 2004; Tapp et al., 2019), it is possible that increased psychological stress may be worsening mental outcomes in post-COVID (specifically LLC) persons. Further, mental outcomes being reported by LLC

persons may worse than those reported by non-COVID persons because of the combination of both viral sequelae and a broad physiological stress response to the pandemic environment.

Rationale and objective

The objective of this study is to contribute to the body of literature regarding persistent mental outcomes following a COVID-19 infection. There is need to distinguish between the profile of mental outcomes in LLC and non-COVID persons given there is likely to be substantial overlap between mental outcomes reported by these two groups of people. Due to the central role of a stress-related physiological response in the mental outcomes being reported, this study hypothesized that stress is primed to moderate the relationship between COVID-19 infection severity and the enduring mental outcomes that are being reported following the acute infection period. In doing so, long COVID as a post-viral syndrome can be distinguished from a non-viral response to the stressful pandemic environment.

Methods

Aims, Research Questions and Hypotheses

The overarching aim of this research was to psychometrically delineate the mental outcomes frequently reported as part of long COVID and to investigate the role of stress in these mental outcomes for the LLC group. These mental outcomes were anxiety, depression, and fatigue. In pursuing this, two specific aims were formulated.

The first aim was to characterize these mental outcomes by investigating, and drawing comparisons between, how these mental outcomes are being reported by LLC and non-COVID participants. The second aim was to investigate if perceived stress played a moderating role in the relationship between COVID-19 infection severity and the mental outcomes associated with long COVID in the LLC group. Since the non-COVID participants

had no history of COVID-19 (and subsequently, no history of infection severity), the moderating role of stress could not be investigated in the same way.

In relation to the first aim, the accompanying research question asked: how are LLC participants, in comparison with non-COVID participants, reporting mental outcomes (namely, depression, fatigue, and anxiety)? The null hypothesis (H_0) was that there was no difference between how these mental outcomes are being reported between LLC and non-COVID participants. Two alternate hypotheses were presented. The first (H_1) was that LLC participants reported more severe and more frequent poor mental outcomes than non-COVID participants. The second (H_2) was that the mental outcomes reported by LLC participants followed similar trends to symptoms of "sickness behaviour" described within the literature.

The second research question, which pertained to the second aim of this research, asked: is the relationship between COVID-19 infection severity and the experience of poor mental outcomes associated with long COVID moderated by perceived stress for the LLC group? In response to this, three alternate hypotheses were suggested relating specifically to the LLC group.

H_0: Perceived stress does not moderate the relationship between COVID-19 infection severity and the experience of poor mental outcomes

H_1: Perceived stress moderates the relationship between COVID-19 infection severity and anxiety

H_2: Perceived stress moderates the relationship between COVID-19 infection severity and depression

H_3: Perceived stress moderates the relationship between COVID-19 infection severity and fatigue

Design

This research used a cross-sectional, correlational design to investigate the mental outcomes associated with long COVID in a LLC and in a non-COVID group, and to assess the moderating role of stress in the relationship between COVID-19 infection severity and poor mental outcomes in the LLC group. Respective mental outcomes were assessed using psychometric measures.

Participants

To determine sample size, a power analysis was conducted using a hypothesised effect size of d = 0.5 in accordance with a similar study conducted by Ravens-Sieberer et al. (2021). Power was set at 0.8, and alpha was assumed to be 0.05. The power analysis projected 612 participants for this study in order for it to be adequately powered. However, due to low participant engagement and due to time constraints of the researchers, only 82 potential participants (67 with a history of COVID-19 and 15 with no COVID-19 history) were recruited for this research via convenience non-probability sampling. 5 participants with a history of COVID-19 did not meet all the inclusion criteria and were removed from the sample. No participants without a COVID-19 history needed to be excluded on this basis.

Eligibility criteria

To be included in the study, participants needed to be between the ages of 18 and 60 years of age and they needed to be residing within South Africa. The geographic limitation of participants was imposed as data from this study was shared with other projects which required participants to potentially participate in person. Subsequently, it was important for participants to reside within South Africa as this is where the researchers were based.

Participants (both with and without a history of COVID-19) were excluded if they indicated that they were currently diagnosed with a cognitive or developmental impairment, central nervous system disease, neurological damage, or neuropathy. Participants were excluded on this basis as these diagnoses were identified as potential confounds to the

accuracy and reliability of findings. Participants were excluded if they indicated that they were currently infected with COVID-19 as this research was specifically focused on comparing post-viral outcomes with mental outcomes in those with no COVID-19 history.

Participant groups

Participants who met the inclusion criteria and completed the respective surveys were divided into two broad groups: the first containing post-COVID participants, and the second containing participants who had never contracted COVID-19 (non-COVID participants). The first group was filtered to include only those who were likely experiencing long COVID (the LLC group). The justification for the latter groups likely long COVID classification, as opposed to definitive long COVID classification, is as follows.

This study is specifically focused on the mental outcomes associated with long COVID. However, not all people who contract COVID-19 go on to develop symptoms of long COVID. Further, as definitive diagnostic criteria for long COVID remains unclear, the present study could not definitively classify post-COVID participants as long COVID participants. As long COVID is a relatively recent and poorly defined syndrome, the possibility was also raised that participants who self-reported that they were not experiencing long COVID might in fact be experiencing long COVID but might not be aware of this due to a poor understanding of what symptoms of the post-viral syndrome are.

To overcome this problem of identifying long COVID participants, post-COVID participants who exhibited a likelihood of experiencing long COVID were included in the LLC group. Likelihood of this was determined in two ways. The LLC group comprised of both participants who self-reported that they were experiencing long COVID (n=27), and those who did not but whose responses on the administered psychometric measures indicated that they may be experiencing poor mental outcomes associated with long COVID (n=30). The former participants are referred to as subjectively confirmed long COVID participants

(SCLCPs). These participants were included irrespective of their psychometric scores and purely based on their self-reported long COVID status. The latter participants are referred to as symptomatic but unaware likely long COVID participants (SULLCPs). Inclusion criteria for the SULLCPs was informed by pre-determined cut-off scores for the respective psychometric measures as indicated by the literature for patient populations.

The reason for the broad inclusion criteria in the LLC group is twofold. First, both SCLCPs and SULLCPs (by virtue of their prior COVID-19 diagnosis) were identified to potentially be experiencing mental outcomes in relation to viral sequelae. Given this, the second reason for including both SCLCPs and SULLCPs within the LLC group is that larger sample sizes improve the accuracy, validity, and generalizability of statistical analysis and subsequently of the results (Tredoux & Durrheim, 2013).

Of the 62 participants who had a confirmed prior diagnosis of COVID-19, 57 were included in the LLC group. Post-COVID participants who were not included in the LLC group were excluded on the basis that they neither self-reported experiencing long COVID nor did their scores on the respective psychometric measures indicate that they may be experiencing poor mental outcomes.

Measures

Perceived Stress Assessment

The Perceived Stress Scale – 10 (PSS-10, Appendix J) is a widely used self-report measure of stress and coping (Cohen et al., 1983). Each of the 10 items is designed measure how stressful participants have found their life circumstances in the last month by asking them to rate their responses to each item using a 5-point Likert scale ranging from 0 (“Never”) to 4 (“Very often”) (Cohen et al., 1983). Scores from each item are summed to create a total score ranging from 0 to 40. Previous research focused on patient populations

have used scores above 27 as a cut-off score to indicate high perceived stress (Cohen et al., 1983; Lipton et al., 2016).

The PSS-10 has frequently been used to assess perceived stress in patient populations such as those with cancer, chronic fatigue syndrome, and post-viral fatigue syndrome (Golden-Kreutz et al., 2004; Johnson et al., 2001; Moss-Morris et al., 2011). It has also been used and validated within the South African context (Makhubela, 2020) and it has been used to assess perceived stress associated with the COVID-19 pandemic (Adamson et al., 2020). Further, high internal consistency reliability and factorial validity have been established for the PSS-10 within the literature (Remor, 2006; Lee, 2012).

Fatigue Assessment

Both the Modified Fatigue Impact Scale (MFIS, Appendix G) (Larson, 2013; Ritvo et al., 1997) and the Fatigue Severity Scale (FSS, Appendix F) (Krupp et al., 1989) were utilised and adapted to measure fatigue. Both scales have been used widely, recommended for further research, and have been used to measure fatigue in post-COVID samples (Friedberg & Jason, 1998; LaChapelle & Finlayson, 1998; Ortelli et al., 2021).

A total FSS score was calculated by summing responses. Participants whose total FSS scores were over 36 were classified as being fatigued. This cut-off is informed by standards used in previous research using patient populations (Gustavsen et al., 2021). The FSS has been found to have high internal consistency and reliability, making it a useful and reliable instrument to assess and quantify fatigue (Armutlu et al., 2007; Valko et al., 2008).

A total MFIS score was calculated by summing all 21 responses. Total MFIS scores range between 0 and 84. Previous research has used a total score of 38 as a cutoff to discriminate fatigued individuals from non-fatigued individuals with a history of viral infection, thus the same cutoff was applied in this research (Kos et al., 2005; Téllez et al.,

2005). The MFIS has been found to be a reliable and valid measure of assessing fatigue in patient populations (Elbers et al., 2012; Ghajarzadeh et al., 2013).

Depression Assessment

The 21-item Beck Depression Inventory II scale (BDI-II, Appendix F) was used to assess depression (Beck et al., 1996). It is a self-report scale used to assess depression symptomatology and severity (Segal et al., 2008). The literature has established that the BDI-II has high internal reliability and validity (Beck et al., 1996; Brown et al., 2000; Segal et al., 2008).

For each participant, a total BDI score was calculated by summing all 21 responses. Total scores between 29-63 indicated severe depression (Beck et al., 1996). For the purposes of this research, LLC participants were considered as exhibiting depressive symptoms if their total BDI -II score was above 20. This cut-off is informed by standards stipulated within the BDI-II Manual (Beck et al., 1996).

Anxiety Assessment

The Beck Anxiety Inventory (BAI, Appendix G) was used to assess anxiety (Beck et al., 1998). It is a widely used self-report measure consisting of 21 items designed to measure the frequency and severity of anxiety symptomatology (Bardhoshi et al., 2016). The 21-items consist of a 4-point Likert scale ranging from 0 (“Never”) to 3 (“Very often/ Severe”) which are summed to result in a score out of 63. For each participant, a total BAI score was calculated by summing all 21 responses. Score interpretation guidelines indicate that scores between 16-25 indicate moderate anxiety, and scores between 26-63 indicate severe anxiety (Beck et al., 1998). For the purposes of this research, LLC participants were considered as exhibiting anxious symptoms if their total BAI score was above 16. This cut-off is informed by standards stipulated by Halfaker et al. (2011) in research on anxiety in patients with

multiple sclerosis. The validity and reliability of the BAI has been established within the literature (Bardhoshi et al., 2016; De Ayala et al., 2005)

Procedure

Participants were recruited using one of two adverts. The first advert (Appendix D) guided those with a confirmed prior diagnosis of COVID-19 to the survey pertaining to post-COVID mental outcomes. The second advert (Appendix E) guided those who did not have a history of COVID-19 to the survey pertaining to general mental outcomes reported by the population. These adverts were both distributed via two platforms. The first was the Student Research Participation Program (SRPP) which is coordinated by the Psychology Department at the University of Cape Town (UCT). The second platform was social media. Both advertisements were distributed via the researcher's social media and in long COVID support groups on social media platforms such as Facebook. Details regarding the purpose of the study and how potential participants could participate were advertised both on the news and on the radio. Potential participants could scan a QR code on the advertisements to be directed to the relevant survey, or they could contact one of the researchers for participation information.

The surveys were conducted online through the platform SogoSurvey. Before participants began the survey, they were provided with an adapted informed consent form (Appendix B; Appendix C). Thereafter, each survey consisted of three core sections. The first section asked participants about their demographic information, including questions regarding their contact details (relevant for SRPP and for debriefing purposes), their age, and medications they may be taking (Appendix N; Appendix O).

The second section asked participants about their self-reported experience of fatigue using the FSS (Appendix F) and MFIS (Appendix G). Fatigue was assessed as it was identified within the literature to be a core symptom reported by both those who had

previously contracted COVID-19 and those who had not. Fatigue is a complex domain to characterize as it has been reported to occur mentally, physically, and cognitively. It was hypothesized that fatigue may be one of the fundamental ways in which symptoms between LLC and non-COVID participants may differ, and further, that LLC participants may be experiencing fatigue in relation to typical "sickness behaviour" (most notably, as physical fatigue and lethargy). Subsequently, two psychometric measures focused on fatigue were administered to participants to try to capture the full extent and variation of fatigue presentation.

The third section of each survey involved the emotional assessment of participants. The first emotional domain assessed was depression using the BDI-II (Appendix H). The second was anxiety using the BAI (Appendix I). The final emotional domain assessed was perceived stress using the PSS (Appendix J). For LLC participants, a fourth section was included in the survey. This section consisted of questions pertaining to the participants' COVID-19 history and experience. Participants were asked questions such as how their COVID diagnosis was obtained, when they were infected with COVID-19, and their level of COVID-19 infection severity (in relation to recovering at home vs. needing to recover in hospital). Each survey took approximately 35 minutes to complete. Once the survey had been completed, participants were emailed a debriefing letter which thanked them for their participation, and which included information regarding the purpose of the study (Appendix K; Appendix L)

Ethical considerations

As the data collected from this study was of a personal and sensitive nature, participants were asked four times throughout the survey if they felt comfortable to continue. It was made clear that there were no negative consequences to the participant if at any point they felt that they wanted to withdraw from the study. Additionally, participants were given

the contact details for mental health services if they felt they needed psychological care after participation. Participants who indicated high BDI scores and specifically, high suicidality scores, were emailed information pertaining to relevant mental health services (Appendix M). The research protocol was approved by UCT's Department of Ethics Review Committee and the Human Research Ethics Committee (reference number: 482/2021, Appendix A)

Statistical analysis

Data from both surveys was exported to RStudio (Version 1.4.1106) for analysis. Data was only included for participants that met either the LLC participant criteria or the non-COVID participant criteria. A subset of data was selected for preliminary data analysis. This included the total scores for the mental outcomes. Significance levels were set at α=0.05 and before analysis could be conducted, all statistical assumptions were checked. Where assumptions were violated, non-parametric statistical procedures were conducted (Tredoux & Durrheim, 2013).

Differences in how mental outcomes are reported by LLC participants and non-COVID participants. For each group, total scores for each of the measures were calculated. The mean for each measure according to the two groups were compared. A correlation matrix was constructed for each of the groups using the pairs.panel function to assess how correlated total scores on the measures were with each other and with specific demographic outcomes. To test the first hypothesis, that LLC participants experienced more frequent and severe mental outcomes than non-COVID participants, an independent samples t-test was conducted for each of the measures. These inferential statistical tests compared the means for each of the groups (LLC and non-COVID) to determine if the differences between the groups were statistically significant.

Exploratory Factor Analysis (EFA) was conducted on each of the measures for both groups to determine where differences in mental outcomes between the two groups lay. For

each measure, the following procedure was conducted. First, a skim function was run to identify the nature in which each item was responded to by participants. Thereafter, a correlation matrix was constructed for each measure to identify relationships between items. Kaiser-Meyer-Olkin factor adequacy values and eigen values were assessed. A Bartlett test of homogeneity of variances was conducted on each of the measures to determine Bartlett's K^2 value. From these preliminary tests, a factor structure was decided upon and was constructed for each of the measures. For each exploratory factor analysis, a varimax rotation was applied to clarify the relationship amongst the factors. The outcome of each group's EFA for each measure were compared to one another to determine where differences in reports of mental outcomes lay.

The role of stress in persistent mental outcomes experienced by LLC participants. An initial linear model was constructed to investigate if there was a relationship between perceived stress and the mental outcomes being reported in the LLC sample. The output of the model was analyzed using the summ function. The results were reported.

Stress was investigated as a potentially moderating factor in the relationship between COVID-19 infection severity and the mental outcomes associated with long COVID (namely, anxiety, depression, and fatigue). To do this, five linear models were constructed, each pertaining to a different mental outcome. These models modelled the moderating effect between perceived stress, the mental outcomes frequently reported, and COVID-19 infection severity. To further investigate the role of stress in the mental outcomes being reported, five stepwise regression models were constructed to investigate the predictors of perceived stress for LLC participants.

Results

Sample characteristics

A total of 82 participants completed the respective surveys. 77 participants met the inclusion criteria and the remaining 5 were excluded from the study. 15 of these participants had no confirmed previous diagnosis of COVID-19 and 62 participants had a confirmed prior diagnosis of COVID-19. Of the 62 post-COVID participants, 57 were included in the LLC group. The total sample of participants for analysis included 72 participants.

Within the LLC sample, COVID-19 infection severity was as follows. 46 participants were able to recover from home, meaning 80.7% of LLC participants experienced a mild COVID-19 infection. 7 recovered at home but felt that they needed to recover in hospital and 2 were admitted to hospital (but were not admitted to the intensive care unit (ICU) and did not need oxygen). This means that 15.8% of LLC participants experienced a moderate COVID-19 infection. 1 participant was admitted to the ICU and 1 participant additionally required oxygen therapy in hospital. Subsequently, only 3.5% of LLC participants experienced a severe COVID-19 infection.

Table 1

Descriptive statistics of included sample (n=72)

	LLC group *n = 57*	**Non-COVID group** *n = 15*	**Total** *n = 72*
Gender			
Female	43 (75.4%)	7 (46.7%)	50 (69.4%)
Male	14 (24.6%)	8 (53.3%)	22 (30.5%)
Age			
Mean age *(SD)*	23.9 *(9.43)*	27.5 *(11.6)*	25.7
Min.	18.00	18.00	18.00
Max.	59.00	57.00	59.00
Education			
Matric/ Undergraduate	39 (68.4%)	5 (33.3%)	44 (61.1%)
Postgraduate	16 (28.1%)	9 (60.0%)	25 (34.7%)
Technical course or diploma	2 (3.5%)	1 (6.7%)	3 (4.2%)

Differences in how mental outcomes are reported by LLC participants and non-COVID participants.

A correlation matrix was constructed to assess the relationship between variables in the non-COVID group and in the LLC group. In the non-COVID group, the following

relationships were identified. Education and BDI total were negatively correlated (r=-0.64). Similarly, education and BAI total scores were negatively correlated too (r=-0.55). This indicates that higher levels of education were correlated with lower levels of anxiety and depression in the non-COVID group. No relationships were identified between perceived stress (PSS total score) and other outcome variables.

In the LLC group, the following relationships were identified. No relationships were identified between education and the other outcome variables. Employment and PSS total was found to be positively correlated (r=0.33). PSS total and BDI total was also found to be positively correlated (r=0.47). This means that higher perceived stress scores were correlated with higher levels of employment and with higher depression. MFIS and BAI were positively correlated (r=0.58). Similarly, MFIS and BDI scores were positively correlated too (r = 0.7). This indicates that more severe fatigue (according to the MFIS) was correlated with more severe anxiety and depression for the LLC group.

For each group, fatigue, depression, anxiety, and perceived stress were psychometrically assessed. The descriptive statistics of each of these measured are presented in Table 2.

Table 2

Descriptive statistics for each measure

	LLC group	**Non-COVID group**
FSS		
$\bar{x}$	51.17	36.73
s	9.16	12.24
Med.	50	35
Min.	36	17
Max.	70	67
MFIS		
$\bar{x}$	72.12	52.27
S	13.09	14.49
Med.	72	51
Min.	43	28
Max.	95	77
BDI-II		
$\bar{x}$	48.15	33.33
s	12.11	12.72
Med.	47	31
Min.	25	21

Max.	78	72
BAI		
$\bar{x}$	43.32	29.87
s	13.05	8.69
Med.	39	26
Min.	25	21
Max.	73	43
PSS		
$\bar{x}$	33.22	32.13
s	4.24	4.03
Med.	32	33
Min.	26	24
Max.	43	37

An independent samples t-test was conducted for each of the measures to compare the means between the LLC group and the non-COVID group. The LLC group scored significantly higher on measures of fatigue, anxiety, and depression than non-COVID participants. At a 95% confidence interval, the p-value was significant ($p<0.05$) for all t-tests conducted (namely, for the FSS, MFIS, BDI-II, BAI, and the PSS). This means that the difference in means between the two groups on each of these measures was found to be statistically significant and unlikely due to chance.

The independent samples *t*-tests determined that a statistically significant difference between the two groups existed on all measures administered, but these tests were limited in their ability to describe where differences in each of the measures lay. Subsequently, an Exploratory Factor Analysis (EFA) was conducted for each of the measures for both groups to assess specifically where differences in mental outcomes lay. Table 3 summarizes the outcome of this. Table 4 details the item structure that was decided upon for each of the measures according to the LLC group and the non-COVID group.

Table 3

Exploratory Factor Analysis of Items within Each Measure

		LLC participants		Non-COVID participants	
Measure	**Outcome**	**Item (M, SD)**	***Description***	**Item (M, SD)**	***Description***
FSS	Highest mean	FSS1 (6.24, 0.88)	*Low motivation when fatigued*	FSS1 (5.07, 1.53)	*Low motivation when fatigued*
	Lowest mean	FSS2 (3.83, 1.60)	*Exercises causes fatigue*	FSS5 (3.07, 1.58)	*Fatigue causes frequent problems*
	Item with most varied responses	FSS8 (4.98, 1.68)	*Fatigue is the most disabling symptom*	FSS9 (3.40, 2.10)	*Fatigue interferes with work, family and social life*
	Item with least varied responses	FSS1 (6.24, 0.88)	*Low motivation when fatigued*	FSS4 (4.33, 1.45)	*Fatigue interferes with physical functioning*
MFIS	Highest mean	MFIS21 (4.02, 0.96)	*Needing more rest*	MFIS2 (3.13, 1.06)	*Difficulty concentrating*
	Lowest mean	MFIS4 (2.90, 0.86)	*Feeling clumsy and uncoordinated*	MFIS18 (2.00, 0.92)	*Difficulty paying attention for long periods of time*
	Item with most varied responses	MFIS20 (3.9, 1.29)	*Limited physical activities*	MFIS21 (2.60, 1.30)	*Needing more rest*
	Item with least varied responses	MFIS1 (3.37, 0.73)	*Feeling less alert*	MFIS3 (2.60, 0.70)	*Unable to think clearly*
BDI-II	Highest mean	BDI16 (3.80, 1.81)	*Changes in sleeping pattern*	BDI16 (2.47, 1.13)	*Changes in sleeping pattern*
	Lowest mean	BDI9 (1.49, 0.68)	*Suicidal thoughts or wishes*	BDI9 (1.13, 0.52)	*Suicidal thoughts or wishes*
	Item with most varied responses	BDI18 (3.39, 1.84)	*Changes in appetite*	BDI18 (2.13, 1.6)	*Changes in appetite*
	Item with least varied responses	BDI19 (2.68, 0.65)	*Difficulty concentrating*	BDI20 (1.60, 0.51)	*Tiredness or fatigue*
BAI	Highest mean	BAI14 (2.78, 0.88)	*Indigestion or abdominal discomfort*	BAI9 (2.00, 1.00)	*Fear of the worst happening*
	Lowest mean	BAI21 (1.56, 0.87)	*Feelings of choking*	BAI1 (1.00, 0.00)	*Numbness or tingling*
	Item with most varied responses	BAI6 (2.17, 1.07) BAI13 (2.37, 1.07)	*Fear of losing control* *Heart pounding*	BAI14 (1.80, 1.08)	*Indigestion or abdominal discomfort*
	Item with least varied responses	BAI16 (1.61, 0.74)	*Difficulty concentrating*	BAI1 (1.00, 0.00)	*Numbness or tingling*
PSS	Highest mean	PSS3 (4.05, 0.97)	*Feeling nervous or stressed*	PSS4 (4.00, 0.93)	*Confidence in being able to handle personal problems*
	Lowest mean	PSS8 (2.44, 0.95)	*Feeling "on top of things"*	PSS2 (2.53, 1.19)	*Feeling as though the important things in life are controllable*
	Item with most varied responses	PSS6 (3.54, 1.19)	*Unable to cope with all that needed to be done*	PSS10 (2.67, 1.29)	*Feeling as though difficulties are piling up and are unable to be controlled*
	Item with least varied responses	PSS7 (3.17, 0.83)	*Ability to control irritations*	PSS5 (3.60, 0.74)	*Feeling as though things are "going your way"*

Table 4

Factor Structure for Each Measure Extracted from Exploratory Factor Analysis

		LLC group		**Non-COVID group**
	No. of factors	*Factor descriptions*	*No. of factors*	*Factor descriptions*
FSS	2	Initiating and maintaining physical activity is limited by fatigue	2	Fatigue interferes in general functioning
		Fatigue as a disabling and interfering symptom		Fatigue is worsened and triggered by physical activity
MFIS	3	Fatigue affects stamina and focus	2	Fatigue affects stamina and concentration
		Fatigue is experienced and worsened in relation to physical activity		Fatigue is experienced cognitively
		Fatigue is reducing capacity to concentrate and to pay attention		
BDI-II	3	Self-destructive and belittling thinking patterns	2	Feelings of worthlessness and sadness
		Irritability and agitation		Cognitive slowing
		Apathy and fatigue		
BAI	2	Psychosomatic experiences of anxiety	3	Feelings of nervousness
		Fearfulness		Physiological experiences of anxiety
		Attention		Fearfulness
PSS	2	Overwhelmed	3	Eustress in relation to work
		Feelings of autonomy and internal locus of control		Feeling autonomous
				Troubled by lack of control of external world

The role of stress in the psychiatric symptoms experienced by LLC participants.

The output of the linear model was not significant ($p = 0.2$). None of the variables were identified as significant contributors to PSS. The residual error value was 3.88 and the adjusted R^2 value was 0.16. This means that the first model explains 16% of the variance observed in the total PSS score of LLC participants.

To assess the extent to which perceived stress was predictive of the other mental outcomes associated with long COVID, stress was investigated as a potential moderating factor. At a 95% confidence interval, no statistically significant moderating effects were found (all p-values > 0.05). To further investigate the role of stress in the mental outcomes associated with long COVID, a series of stepwise regression models were constructed.

Perceived stress was identified as a statistically significant predictor only of depression in the LLC group ($p = 0.05$, $SE = 0.29$).

An additional stepwise regression model was constructed to investigate the predictors of perceived stress in LLC participants. Age ($p = 0.01$, $SE = 0.05$, intercept = -0.12) and depression ($p = 0.00$, $SE = 0.05$, intercept = 0.18) were identified as statistically significant. Employment, monthly household income and level of education were not identified as predictive of stress, nor were they identified as predictive of the other mental outcomes investigated.

Discussion

Using subjective psychometric measures, this study aimed to characterize the mental outcomes frequently reported as part of the post-viral syndrome, long COVID, and to differentiate these symptoms from a broad stress response to the pandemic environment. The results suggest that LLC participants display and experience more severe mental outcomes than non-COVID participants. Additionally, this study aimed to investigate the moderating role of perceived stress in the mental outcomes of long COVID in a LLC sample. The results suggest that perceived stress does not play a moderating role between COVID-19 infection severity and the mental outcomes of long COVID in the LLC sample. This may reflect that worse mental outcomes in the LLC group were likely more related to viral sequelae than to a stress response to the pandemic. Within this discussion, these findings are discussed in reference to the evidence established in the literature, the limitations of this study, and what the findings suggest for future long COVID research.

Psychometrically delineating the mental outcomes associated with long COVID

Mental outcomes related to anxiety, depression, and fatigue have frequently been reported by both those who have contracted COVID-19 and those who have not (Ettman et al., 2020; Hyland et al., 2020; Shevlin et al., 2020). Due to common aetiological mechanisms

that underlie these mental outcomes, it was suggested that they may be associated with a broad physiological stress response to the pandemic environment rather than purely viral sequelae. Subsequently, there was potential for similarities in these mental outcomes between LLC participants and non-COVID participants. However, the results from this study found statistically significant differences in the presentation of these symptoms between the two groups of participants. Each are discussed.

Fatigue

Fatigue was reported with greater severity and less variation across both psychometric measures for LLC participants compared to non-COVID participants. LLC participants reported experiencing fatigue in accordance with how fatigue is typically experienced as part of sickness behaviour. Sickness behaviour symptoms, like those indicated by LLC participants, include physical lethargy and general mental tiredness (Hart, 1998). In this way, there are similarities between these symptoms and symptoms of depression (Andreasson et al., 2016). Sickness behaviour symptoms result as by-products of a physiological attempt to conserve energy and to fight pathogens (Aubert, 1999). This presented as difficulties in initiating and maintaining physical and mental activity, a reduction in attention, and by participants reporting that they needed more rest. Conversely, non-COVID participants did not report fatigue as predominantly in this way. Rather than being marked by physical lethargy, non-COVID participants reported fatigue in relation to a decline in motivation.

However, motivational declines were found to be relatively consistent among both LLC and non-COVID participants. It is suggested that declines in motivation in LLC and non-COVID participants may be resulting from common environmental factors related to the pandemic. Evidence from a survey on Canadian workers found that approximately 36% of workers reported declines in motivation due to the pandemic (Wilson, 2020). Wilson (2020) attributes this to a manifestation of emotional exhaustion stemming from adjustments to a

virtual work-space, and the increasingly interconnected nature of home-life with work-life. For LLC persons, this experience of motivational decline in addition to symptoms of sickness behaviour may be contributing to more severe reports of fatigue.

Depression

While LLC participants displayed consistently higher depressive scores, the presentation and severity of depressive symptoms across both groups was found to be similar. Total scores for both groups were classified as severe according to standards stipulated within the BDI-II Manual (Beck et al., 1996). There were also similar trends in how participants from both groups reported depressive symptoms although LLC participants reported higher scores for each of the items.

Commonalities between the two groups were found in that neither group indicated suicidality and both groups reported experiencing changes in their sleeping patterns. This finding matches previous findings within the literature that changes in sleeping behaviours have been observed across the population due to the COVID-19 pandemic environment (Robillard et al., 2020). These changes in sleeping patterns, while likely due in part to COVID sequelae for the LLC group, may also be due to factors such as higher stress levels and maladaptive coping strategies such as heavier alcohol use and more frequent television exposure that were found to be reported within the literature (Beck et al., 2020; Stanton et al., 2020; Robillard et al., 2020).

Despite this, there were important differences in how these changes in sleeping patterns related to fatigue and tiredness. Non-COVID participants displayed the least variation on items pertaining to tiredness and fatigue, indicating that although changes in sleeping patterns were reported, it does not necessitate that non-COVID participants were more fatigued. This suggests that non-COVID participants may be feeling more rested as a result of their change in sleeping patterns. Conversely, for LLC participants, a change in

sleeping patterns might be due to the experience of sickness behaviour (Hart, 1998), and partly a result from increased fatigue (indicated by the FSS and MFIS).

Anxiety

LLC participants are experiencing more severe anxiety than non-COVID participants. However, LLC participants showed more variation in their anxiety scores than non-COVID participants. This suggests that the experience of anxiety as part of long COVID is more varied that the experience of anxiety in a non-COVID population. This variation in reports of anxiety for LLC participants is discussed.

Previous research has found that approximately 50% of hospitalized COVID-19 survivors experienced increased anxiety following hospital discharge (Fernàndez-de-las-Peñas et al., 2021). Only 4 LLC participants were hospitalized whilst 80.7% of LLC participants did not require hospitalization. Subsequently, unlike findings within the literature COVID-19 infection severity did not appear to be related to anxiety severity, although this may be due to a skewed sample. Anxiety in those who were not hospitalized may be due to an increase in health-related anxiety across international populations as identified by the literature (Gallagher et al., 2020; Wallace et al., 2020). However, further research is needed to understand the factors underlying variation in anxiety scores in LLC participants.

Unlike non-COVID participants, LLC participants reported predominantly experiencing symptoms of anxiety psychosomatically. In LLC participants, the item with the highest mean pertained to indigestion and abdominal discomfort. Conversely, this item was reported with the highest variation by non-COVID participants. This indicates that anxiety may be experienced in a more marked psychosomatic way in a long COVID sample than in a non-COVID sample. The literature suggests that this may be due to a prior physiological experience of the illness and a subsequent heightened awareness for physiological sensations

similar to those experienced during the acute phase of COVID-19 infection (Amdal et al., 2021).

Perceived stress as a moderating variable in mental outcomes of LLC participants

The COVID-19 pandemic has been frequently reported to result in higher levels of negatively perceived stress across the population (Ettman et al., 2020; Hyland et al., 2020; Sher, 2021; Shevlin et al., 2020). The findings of this study corroborated this trend in the literature in that the mean perceived stress scores for both LLC participants and non-COVID participants were high. This suggests that negatively perceived stress was found to be high across both groups of participants, irrespective of their COVID-19 history. Interestingly, perceived stress was also found to be predictive of depressive symptoms in LLC participants. Perceived stress may be contributing to the changes in sleeping patterns observed in LLC participants and potentially in non-COVID participants too although further research and statistical analysis is required to clarify this relationship.

However, contrary to what was hypothesised, the mental outcomes of long COVID were found neither to be associated with nor exacerbated by stress. This finding supports theories that suggest that post-viral syndromes manifest because of the biochemical and pathophysiological mechanisms of viral sequelae rather than because of a psychological response to the viral illness or the environmental conditions surrounding it (Preedy et al., 1993).

Only 3.5% of LLC participants experienced a severe COVID-19 infection but all 57 participants indicated that they were experiencing persistent symptoms beyond the acute infection period. COVID-19 infection severity subsequently does not seem to predict mental outcomes post-virally. This finding supports previous research which indicated that symptoms of long COVID are being reported both by those who experienced a severe

COVID-19 infection and those who experienced a mild COVID-19 infection (Graham et al., 2021; Huang et al., 2021; Kingstone et al., 2020; Negrini et al., 2021; Townsend et al., 2020).

Despite this, the moderating role of stress in the mental outcomes being reported was investigated. Stress was theorized to moderate the relationship between COVID-19 infection severity and post-viral mental outcomes. However, no statistically significant relationships were found. This indicates that stress does not moderate the relationship between COVID-19 infection severity and mental outcomes persisting beyond the acute phase of COVID-19 infection.

Limitations

The present study has several limitations. First, the sample size was insufficient according to the preliminary power analysis that was conducted. This means that the findings of this study are likely to be skewed and are limited in their generalizability. Additionally, the LLC group was much larger than the non-COVID group of participants. This limited the ability to meaningfully compare results on these two groups. Long COVID participants were also not definitively identified, and rather the study relied on participants that likely were experiencing long COVID. Broadly, the fourth limitation was that survey responses may not have accurately reflected participants responses. This is due to two reasons.

Due to the surveys being online and likely conducted on participants' cellular devices, there is a high chance of participants falling into a response bias. This is when participants blindly answer questions without engaging with what the question is asking. Secondly, the psychometric measures administered for the purposes of this study may not have adequately encompassed the full breadth and depth of the mental outcomes being experienced particularly in relation to the COVID-19 pandemic. This has the potential to have limited the findings. Additionally, as long COVID remains difficult to distinctively diagnose, the cut-offs

that were applied for the LLC group may have been too narrow or conversely, too broad, to encapsulate the full range of symptoms experienced as part of long COVID.

The final limitation of this research was that most participants were in their early 20s. This was largely due to the medium of recruitment utilized by this study. By using the UCT SRPP program, most participants participated in the research as part of the requirements for the undergraduate Psychology degree. Due to this, many of the participants were between the ages of 18 and 22. As data was collected around university exam time, this may have led participants to exaggerate their symptoms due to exam-related stress.

Future research

The current findings highlight the need for future research to build on the proposed characterizations of the mental outcomes of long COVID. A more varied sample is required for the results of the research to be generalizable. By using a larger sample size and by extending the measures administered to participants, a more thorough analysis and contextualization of symptoms can be achieved. Although this study sought to investigate the role of perceived stress on the mental outcomes associated with long COVID, there is also a need to investigate this relationship for non-COVID persons. Additionally, this study may have been limited by its use of LLC participants, the trends in the reports of this groups mental outcomes should be used as a basis for guiding future research on long COVID. In doing so, a clearer understanding of long COVID as a distinct post-viral syndrome can be achieved.

Conclusion

This study sought to characterize and psychometrically delineate the mental outcomes that persist beyond the acute infection period of COVID-19. Findings indicate that LLC participants experienced mental outcomes (namely in terms of anxiety, fatigue, and depression) that were more severe than non-COVID participants. Additionally, mental

outcomes reported by LLC participants appeared to follow trends of "sickness behaviour" identified within the literature. Specifically, a strong theme across the mental outcomes reported by LLC participants was that they were experiencing a lack of energy and marked lethargy. Perceived stress was found not to be a moderating variable in the relationship between COVID-19 infection severity and the mental outcomes reported by LLC participants.

Acknowledgements

I would like to extend my sincerest gratitude to Dr Donné Minné and to Altay Yüce Turan for their invaluable feedback and guidance throughout this thesis. I would also like to thank my mom, dad, and Erin for their continued encouragement, reassurance, and support. I am truly grateful to the people who have surrounded me and who have fortified me as I have navigated this challenging year.

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Appendix A

Ethical Clearance

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

01 October 2021

HREC REF: 482/2021

Prof M Solms
Department of Psychology
PD Hahn Building-UCT
Email: Mark.solms@uct.ac.za
Student: Trnalt001@myuct.ac.za

Dear Prof Solms

PROJECT TITLE: A MIXED METHODS INVESTIGATION OF THE MENTAL ASPECTS OF POST-COVID/LONG COVID FATIGUE (MASTER'S DEGREE - MR ALTAY TURAN)

Thank you for your response letter, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020: 06 July 2020 & 01 July 2021.

Approval is granted for one year until the 30 October 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Mr Altay Turan will also be involved in this study.

Please quote the HREC REF 482/2021 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

HREC/REF 482/2021sa

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC/REF 482/2021sa

Appendix B

Online Questionnaire Consent Form for non-COVID participants

We are a team of researchers studying the long-term effects of the COVID-19 Virus. The overall purpose of this research is to characterise the mental aspects of fatigue that those with Long Covid present with. This questionnaire seeks to collect important data about your fatigue, emotional state, and cognitive levels as a means of comparison with Long Covid participants. If you, or anyone you know believes they have long Covid, please email the researchers so we may recruit you for the long Covid participant group. All mandatory questions only require you to select an option or one-word answer.

It should take a maximum of 35 minutes to complete and it is likely you will finish far sooner. We have inserted break pages between sections for your convenience. You may use these break pages as an opportunity to take a break; as long the browser tab is kept open, and you return to the survey within an hour your data will be retained.

There are risks involved with the questionnaire, as there are questions on mental health that will ask about suicidality, emotional strain, and stress. There are also questions on your overall physical and mental state. We have left our email contact at the bottom of this consent form; please email us if you experience distress while answering this questionnaire. We have also inserted links and contacts for mental health advocacy groups that can provide counselling at the end of this form and throughout the questionnaire.

This questionnaire will record some important data for this study, including your demographic information. Additionally, we will need your contact details to send you a de-briefing email. None of this information will be disclosed to any person outside of this study. At study completion, records shall also be stored in a two-factor authenticated drive, only accessible to researchers.

In the next few days after you complete the survey, you will receive a de-briefing email thanking you for your participation, with a list of support contacts and a reiteration of the rationale of the study. If you do submit a response on this survey, you will also receive an aggregation of the research findings early next year once the findings have been analysed. After this point, your contact information shall be removed from our database.

To start the survey, please give your consent below, and confirm that you meet the eligibility criteria. This is not binding - you may choose to stop the questionnaire at any time. The next section will then record biographic and demographic information before beginning the questionnaire. If any of this is unclear, please contact us at the email addresses listed below. Thank you for your time.

Best

Altay Yuce Turan

Donné Minné

Madeleine Ashton

Arjun Maharaj

Email Contacts:

donneminne.za@gmail.com - Dr Donné Minné

trnalt001@myuct.ac.za - Altay Yuce Turan

Mental Health Referrals:

If you are needing a referral to a psychologist, psychiatrist or support group, we encourage you to call The South African Depression and Anxiety Group (SADAG) on

011 234 4837 or 0800 20 50 26 and speak to a trained counsellor who can assist you further. Or alternatively email Zane on zane@sadag.org

You are also encouraged to email one of the Principal Investigators in this study, Dr Donné Minné, who is a registered neuropsychologist with the HPCSA and who will be able to provide you with a consultation should you be requiring one.

Donneminne.za@gmail.com

(PS 0150380)

We would also like to draw your attention to a number of other mental health support resources available to you:

Dr Reddy's Help Line

0800 21 22 23

Cipla 24hr Mental Health Helpline

0800 456 789

Pharmadynamics Police &Trauma Line

0800 20 50 26

Adcock Ingram Depression and Anxiety Helpline

0800 70 80 90

ADHD Helpline

0800 55 44 33

Department of Social Development Substance Abuse Line 24hr helpline

0800 12 13 14

SMS 32312

Suicide Crisis Line

0800 567 567

SADAG Mental Health Line

011 234 4837

Akeso Psychiatric Response Unit 24 Hour

0861 435 787

Cipla Whatsapp Chat Line

(9am-4pm, 7 days a week)

076 882 2775

24 hour Healthcare Workers Care Network Helpline

0800 21 21 21

SMS 43001

NPOWERSA Helpline

0800 515 515

SMS 43010

For affordable counselling, please contact the Counselling Hub

021 462-3902 (landline) or 067 235-0019 (mobile)

For non-appointment enquiries please email info@counsellinghub.org.za

Appendix C

Online Questionnaire Consent Form for post-COVID participants

We are a team of researchers studying the long-term effects of the COVID-19 Virus. The overall purpose of this research is to characterise the mental aspects of fatigue that those with Long Covid present with. This questionnaire seeks to collect important data about your fatigue, emotional state, cognitive levels and understand whether you may have Long Covid symptoms. All mandatory questions only require you to select an option or one-word answer. Additionally, this survey will assess your eligibility for a second phase of research.

It should take a maximum of 35 minutes to complete and it is likely you will finish far sooner. We have inserted break pages between sections for your convenience. You may use these break pages as an opportunity to take a break, or take a break at any point during the survey; as long as you keep the browser tab open, and return to the survey within an hour your data will be retained.

There are risks involved with the questionnaire, as there are questions on mental health that will ask about suicidality, emotional strain, and stress. There are also questions on your overall physical and mental state. Additionally, there are optional open-ended questions where we ask about your Long Covid experience, which may lead to recalling traumatic memories. We have left our email contact at the bottom of this consent form; please email us if you experience distress while answering this questionnaire. We have also inserted links and contacts for mental health advocacy groups that can provide counselling at the end of this form and throughout the questionnaire.

This questionnaire will record some important data for this study, including your demographic information. Additionally, we will need your contact details to send you a de-briefing email, and so that we can recruit you for the second phase of the study if eligible.

None of this information will be disclosed to any person outside of this study. At study completion, records shall also be stored in a two-factor authenticated drive, only accessible to researchers.

In the next few days after you complete the survey, you will receive a de-briefing email thanking you for your participation, with a list of support contacts and a reiteration of the rationale of the study, and an invite to participate in the next phase of research if eligible. If you do submit a response on this survey, you will also receive an aggregation of the research findings early next year once the findings have been analysed. After this point, your contact information shall be removed from our database.

To start the survey, please give your consent below, and confirm that you meet the eligibility criteria. This is not binding - you may choose to stop the questionnaire at any time. The next section will then record biographic and demographic information before beginning the questionnaire. If any of this is unclear, please contact us at the email addresses listed below. Thank you for your time.

Best

Altay Yuce Turan

Donné Minné

Madeleine Ashton

Arjun Maharaj

Email Contacts:

donneminne.za@gmail.com - Dr Donné Minné

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Donneminne.za@gmail.com

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0800 567 567

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011 234 4837

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(9am-4pm, 7 days a week)

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For affordable counselling, please contact the Counselling Hub

021 462-3902 (landline) or 067 235-0019 (mobile)

For non-appointment enquiries please email info@counsellinghub.org.za

Appendix D

Advert for post-COVID participants

Appendix E

Advert for non-COVID participants

Appendix F

Fatigue Severity Scale (FSS) (adapted from Krupp et al., 1989)

Date: _____ **Participant Number: ____**

Read and Circle a Number	Strongly Disagree -> Strongly Agree
1. My motivation is lower when I am fatigued.	1, 2, 3, 4, 5, 6, 7
2. Exercise brings on my fatigue.	1, 2, 3, 4, 5, 6, 7
3. I am easily fatigued.	1, 2, 3, 4, 5, 6, 7
4. Fatigue interferes with my physical functioning.	1, 2, 3, 4, 5, 6, 7
5. Fatigue causes frequent problems for me.	1, 2, 3, 4, 5, 6, 7
6. My fatigue prevents sustained physical functioning.	1, 2, 3, 4, 5, 6, 7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1, 2, 3, 4, 5, 6, 7
8. Fatigue is among my most disabling symptoms.	1, 2, 3, 4, 5, 6, 7
9. Fatigue interferes with my work, family, or social life	1, 2, 3, 4, 5, 6, 7

The FSS is a questionnaire that measures your fatigue levels. It consists of nine statements that refer to the experience you may have with fatigue. Please read each statement, consider if it applies to you, and then circle a number from 1 to 7 according to how accurately you believe it describes your fatigue over the past seven days, and the extent that you agree or disagree with the statement's description of your fatigue. A low value (for example, 1) reflects strong disagreement, whereas a high value (e.g., 7) reflects strong agreement. You must circle a number for every statement.

The Fatigue Severity Scale Key:

A summated score lower than 36 suggests that the respondent may not suffer from fatigue.

A summated score of 36 and higher suggests that the respondent may require an evaluation by a physician.

Appendix G

Modified Fatigue Impact Scale (adapted from Ritvo et al., 1997, and https://www.sralab.org/rehabilitation-measures/modified-fatigue-impact-scale)

The MFIS is a questionnaire designed to evaluate how your fatigue has affected your experience. Please read the statements, and then circle the number which best reflects how regularly fatigue has impacted you in this way, over the past four weeks. If you require assistance with writing your response, inform the administrator of the appropriate number. It is required to answer every question. If unsure of which answer to select, base your final choice of which one best describes your experience. Please inform the administrator if you do not understand any aspects of the statements.

Because of my fatigue during the past 4 weeks:

		Never	Rarely	Sometimes	Often	Almost Always
1.	I have been less alert.	0	1	2	3	4
2.	I have had difficulty paying attention for long periods of time.	0	1	2	3	4
3.	I have been unable to think clearly.	0	1	2	3	4
4.	I have been clumsy and uncoordinated.	0	1	2	3	4
5.	I have been forgetful.	0	1	2	3	4
6.	I have had to pace myself in my physical activities.	0	1	2	3	4
7.	I have been less motivated to do anything that requires physical effort.	0	1	2	3	4
8.	I have been less motivated to participate in social activities.	0	1	2	3	4
9.	I have been limited in my ability to do things away from home.	0	1	2	3	4
10.	I have trouble maintaining physical effort for long periods.	0	1	2	3	4
11.	I have had difficulty making decisions.	0	1	2	3	4
12.	I have been less motivated to do anything that requires thinking	0	1	2	3	4
13.	My muscles have felt weak	0	1	2	3	4
14.	I have been physically uncomfortable.	0	1	2	3	4
15.	I have had trouble finishing tasks that require thinking.	0	1	2	3	4
16.	I have had difficulty organizing my thoughts when doing things at home or at work.	0	1	2	3	4
17.	I have been less able to complete tasks that require physical effort.	0	1	2	3	4

	Never	Rarely	Sometimes	Often	Almost Always
18. My thinking has been slowed down.	0	1	2	3	4
19. I have had trouble concentrating.	0	1	2	3	4
20. I have limited my physical activities.	0	1	2	3	4
21. I have needed to rest more often or for longer periods.	0	1	2	3	4

Instructions for Scoring the MFIS

Items on the MFIS can be aggregated into three subscales (physical, cognitive, and psychosocial), as well as into a total MFIS score. All items are scaled so that higher scores indicate a greater impact of fatigue on a person's activities.

Physical Subscale

This scale can range from 0 to 36. It is computed by adding raw scores on the following items: 4+6+7+10+13+14+17+20+21

Cognitive Subscale

This scale can range from 0 to 40. It is computed by adding raw scores on the following items: 1+2+3+5+11+12+15+16+18+19

Psychosocial Subscale

This scale can range from 0 to 8. It is computed by adding raw scores on the following items: 8+9

Total MFIS Score

The total MFIS score can range from 0 to 84. It is computed by adding scores on the physical, cognitive, and psychosocial subscales.

Appendix H

Beck Depression Inventory-II (adapted from Beck et al., 1996)

This questionnaire has 21 groups of statements. Please read each statement carefully, before selecting out the one statement in each group which most appropriately describes the way you've felt over the past two weeks, including today. If multiple statements apply to your experience, pick the one that has the highest number in the relevant group. Do not choose multiple answers for any group, including item 16 (sleep pattern changes), or item 18 (Changes in Appetite)

1. **Sadness**
   0. I do not feel sad.
   1. I feel sad much of the time.
   2. I am sad all the time.
   3. I am so sad or unhappy that I can't stand it.
2. **Pessimism**
   0.I am not discouraged about my future.
   1.I feel more discouraged about my future than I used to.
   2. I do not expect things to work out for me.
   3. I feel my future is hopeless and will only get work
3. **Past Failure**
   0. I do not feel like a failure.
   1. I have failed more than I should have.
   2. As I look back, I see a lot of failures.
   3. I feel I am a total failure as a person.
4. **Loss of Pleasure**
   0. I get as much pleasure as I ever did from the things I enjoy.
   1. I don't enjoy things as much as I used to.
   2. I get very little pleasure from the things I used to enjoy.
   3. I can't get any pleasure from the things I used to enjoy.
5. **Guilty Feelings**
   0. I don't feel particularly guilty.
   1. I feel guilty over many things I have done or should have done.
   2. I feel quite guilty most of the time.
   3.I feel guilty all of the time.

6. **Punishment Feelings**

0. I don't feel I am being punished.

1.I feel I may be punished.

2.I expect to be punished.

3.I feel I am being punished.

7. **Self-Dislike**

0.I feel the same about myself as ever.

1.I have lost confidence in myself.

2.I am disappointed in myself.

3.I dislike myself.

8. **Self-Criticalness**

0. I don't criticize or blame myself more than usual.

1. I am more critical of myself than I used to be.

2. I criticize myself for all of my faults.

3.I blame myself for everything bad that happens.

9. **Suicidal Thoughts or Wishes**

0. I don't have any thoughts of killing myself.

1. I have thoughts of killing myself, but I would not carry them out.

2.I would like to kill myself.

3.I would kill myself if I had the chance.

10. **Crying**

0.I don't cry anymore than I used to.

1.I cry more than I used to.

2.I cry over every little thing.

3.I feel like crying, but I can't.

11. **Agitation**

0.I am no more restless or wound up than usual

1.I feel more restless or wound up than usual.

2.I am so restless or agitated, it's hard to stay still.

3.I am so restless or agitated that I have to keep moving or doing something.

12. **Loss of Interest**

0.I have not lost interest in other people or activities.

1. I am less interested in other people or things than before.

2. I have lost most of my interest in other people or things.

3. It’s hard to get interested in anything.

13. Indecisiveness

0.I make decisions about as well as ever.

1.I find it more difficult to make decisions than usual.

2.I have much greater difficulty in making decisions than I used to.

3.I have trouble making any decisions.

14. Worthlessness

0.I do not feel I am worthless.

1. I don't consider myself as worthwhile and useful as I used to.

2.I feel more worthless as compared to others.

3.I feel utterly worthless.

15. Loss of Energy

0.I have as much energy as ever.

1.I have less energy than I used to have.

2.I don't have enough energy to do very much.

3.I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0.I have not experienced any change in my sleeping.

1a I sleep somewhat more than usual.

1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.

2b I sleep a lot less than usual.

3a I sleep most of the day.

3b I wake up 1-2 hours early and can't get back to sleep.

17. Irritability

0.I am not more irritable than usual.

1.I am more irritable than usual.

2.I am much more irritable than usual.

3.I am irritable all the time.

18. Changes in Appetite

0.I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.

1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.

2b My appetite is much greater than usual.

3a I have no appetite at all.

3b I crave food all the time.

19. Concentration Difficulty

0.I can concentrate as well as ever.

1.I can't concentrate as well as usual.

2.It's hard to keep my mind on anything for very long.

3. I find I can't concentrate on anything

20. Tiredness or Fatigue

0.I am no more tired or fatigued than usual.

1.I get more tired or fatigued more easily than usual.

2.I am too tired or fatigued to do a lot of the things I used to do.

3.I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0.I have not noticed any recent change in my interest in sex.

1.I am less interested in sex than I used to be.

2.I am much less interested in sex now.

3.I have lost interest in sex completely.

Total Score: ___

Appendix I

Beck Anxiety Inventory (BAI) (adapted from Beck et al., 1988)

This questionnaire is designed to measure how you've been feeling over the past week, including today. Please rate how much you have been bothered by each symptom, on a 4-point scale where 0 represents *Not at all,* to 3 representing, *Severely -I could barely stand it.*

Item	Rating			
1.) Numbness or tingling	0	1	2	3
2.) Hands trembling	0	1	2	3
3.) Feeling hot	0	1	2	3
4.) Shaky	0	1	2	3
5.) Wobbliness in legs	0	1	2	3
6.) Fear of losing control	0	1	2	3
7.) Unable to relax	0	1	2	3
8.) Difficulty breathing	0	1	2	3
9.) Fear of the worst happening	0	1	2	3
10.) Fear of dying	0	1	2	3
11.) Dizzy or lightheaded	0	1	2	3
12.) Scared	0	1	2	3
13.) Heart pounding or racing	0	1	2	3
14.) Indigestion or discomfort in abdomen	0	1	2	3

15.) Unsteady	0	1	2	3
16.) Faint	0	1	2	3
17.) Terrified	0	1	2	3
18.) Flushed	0	1	2	3
19.) Nervous	0	1	2	3
20.) Sweating (not due to heat)	0	1	2	3
21.) Feelings of choking	0	1	2	3

Appendix J

Perceived Stress Scale (PSS) (adapted from Cohen et al., 1983)

The questions in this scale ask you about your feelings and thoughts during THE LAST MONTH. In each case, please indicate your response by placing an "X" over the circle representing HOW OFTEN you felt or thought a certain way.

	Never	Almost Never	Sometimes	Fairly Often	Very Often
	0	1	2	3	4
1. In the last month, how often have you been upset because of something that happened unexpectedly?	○	○	○	○	○
2. In the last month, how often have you felt that you were unable to control the important things in your life?	○	○	○	○	○
3. In the last month, how often have you felt nervous and "stressed"?	○	○	○	○	○
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	○	○	○	○	○
5. In the last month, how often have you felt that things were going your way?	○	○	○	○	○
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	○	○	○	○	○
7. In the last month, how often have you been able to control irritations in your life?	○	○	○	○	○
8. In the last month, how often have you felt that you were on top of things?	○	○	○	○	○
9. In the last month, how often have you been angered because of things that were outside your control?	○	○	○	○	○
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	○	○	○	○	○

Appendix K

Debriefing email for post-COVID participants

Dear Participant,

We would like to thank you for participating in our survey.

Our research aims to characterise the mental aspects of long COVID. We will send you an aggregation of our findings upon completion of the research. If you would like to opt out of this, please let us know.

Further, if participation in our study caused you any discomfort or if you have any concerns about the survey, please email us at the following: covidandthebrain@gmail.com

Additionally, if our survey caused you to feel any mental or emotional stress, please refer to the list of mental health resources at the end of this email

Regards

The long covid mental fatigue research team

If you are needing a referral to a psychologist, psychiatrist or support group, we encourage you to call The South African Depression and Anxiety Group (SADAG) on 011 234 4837 or 0800 20 50 26 and speak to a trained counsellor who can assist you further. Or alternatively email Zane on zane@sadag.org

You are also encouraged to email one of the Principal Investigators in this study, Dr Donné Minné, who is a registered neuropsychologist with the HPCSA and who will be able to provide you with a consultation should you be requiring one.

Donneminne.za@gmail.com

(PS 0150380) **We would also like to draw your attention to a number of other mental health support resources available to you:**

Dr Reddy's Help Line
0800 21 22 23

Cipla 24hr Mental Health Helpline
0800 456 789

Pharmadynamics Police &Trauma Line
0800 20 50 26

Adcock Ingram Depression and Anxiety Helpline
0800 70 80 90

ADHD Helpline
0800 55 44 33

Department of Social Development Substance Abuse Line 24hr helpline
0800 12 13 14
SMS 32312

Suicide Crisis Line
0800 567 567

SADAG Mental Health Line
011 234 4837

Akeso Psychiatric Response Unit 24 Hour
0861 435 787

Cipla Whatsapp Chat Line
(9am-4pm, 7 days a week)
076 882 2775

24 hour Healthcare Workers Care Network Helpline
0800 21 21 21
SMS 43001

NPOWERSA Helpline
0800 515 515
SMS 43010

For affordable counselling, please contact the Counselling Hub

021 462-3902 (landline) or 067 235-0019 (mobile)

For non-appointment enquiries please email info@counsellinghub.org.za

Appendix L

Debriefing email for non-COVID participants

Dear Participant,

We would like to thank you for participating in our survey.

Our research aims to characterise the mental aspects of long COVID. We will send you an aggregation of our findings upon completion of the research. If you would like to opt out of this, please let us know.

If you contract a COVID-19 infection in the future and are willing to provide further data of your experience, please contact us.

Further, if participation in our study caused you any discomfort or if you have any concerns about the study, please email us at the following:

covidandthebrain@gmail.com

Additionally, if our survey caused you to feel any mental or emotional stress, please refer to the list of mental health resources at the end of this email

Regards

The long covid mental fatigue research team

If you are needing a referral to a psychologist, psychiatrist or support group, we encourage you to call The South African Depression and Anxiety Group (SADAG) on 011 234 4837 or 0800 20 50 26 and speak to a trained counsellor who can assist you further. Or alternatively email Zane on zane@sadag.org

You are also encouraged to email one of the Principal Investigators in this study, Dr Donné Minné, who is a registered neuropsychologist with the HPCSA and who will be able to provide you with a consultation should you be requiring one.

Donneminne.za@gmail.com

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Appendix M

Email sent to participants with high BDI scores/ Suicidality Scores

Dear

Recently, you filled out a survey for long COVID research. This email is about how we noticed that some of your responses indicated you are at particularly high risk for mental health issues.

(included for students) I wanted to point out again the mental health referral sources in our study, (attached at the end) and also suggest making an appointment with SWS counsellors if you can?

https://outlook.office365.com/owa/calendar/STUDENTWELLNESSSERVICEPSYCHOLOGICALSERVICES@mscloudtest.uct.ac.za/bookings/

DSA - STUDENT WELLNESS SERVICE - COUNSELLING SERVICES - You can book online!

You can now book and manage appointments using our booking page.

outlook.office365.com

We wish you fortitude and health. Please see the referral list below.

Mental Health Referrals:

If you are needing a referral to a psychologist, psychiatrist or support group, we encourage you to call The South African Depression and Anxiety Group (SADAG) on 011 234 4837 or 0800 20 50 26 and speak to a trained counsellor who can assist you further. Or alternatively email Zane on zane@sadag.org

You are also encouraged to email one of the Principal Investigators in this study, Dr Donné Minné, who is a registered neuropsychologist with the HPCSA and who will be able to provide you with a consultation should you be requiring one.

Donneminne.za@gmail.com

(PS 0150380)**We would also like to draw your attention to a number of other mental health support resources available to you:**

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For non-appointment enquiries please email info@counsellinghub.org.za

Appendix N

Demographic information questions (given to post-COVID participants)

✱ 4. What is your full (legal) name?
(First name(s) Surname)

Characters Remaining: 100

5. What is your student number, if applicable? (Necessary for UCT SRPP)

Characters Remaining: 100

✱ 6. What is your phone number?

Characters Remaining: 100

✱ 7. What is your e-mail address?

Characters Remaining: 100

✱ 8. Do you know what test confirmed your COVID-19 diagnosis?

- ○ Nose swab
- ○ Laboratory test (serotology)
- ○ Other (Please specify)

✱ 9. Are you currently taking any of the following medications? (Check all that apply)

- ☐ I am not taking any medication
- ☐ Antidepressants (e.g. Zoloft, Prozac, Sarafem, Celexa, Paxil, Brisdelle, Pexeva, Lexapro, Luvox, Viibryd)
- ☐ Anti-anxiety medication (e.g. Alzam, Azor, Xanax, Zopax, Lexotan)
- ☐ Allergy medication (e.g. antihistamines)
- ☐ Blood pressure medication
- ☐ Other (Please specify)

Appendix O

Demographic information questions (given to non-COVID participants)

✱ 4. What is your full (legal) name?
(First name(s) Surname)

Characters Remaining: 100

5. What is your student number, if applicable? (Necessary for UCT SRPP)

Characters Remaining: 100

✱ 6. What is your phone number?

Characters Remaining: 100

✱ 7. What is your e-mail address?

Characters Remaining: 100

✱ 8. Are you currently taking any of the following medications? (Check all that apply)

- [ ] I am not taking any medication
- [ ] Antidepressants (e.g. Zoloft, Prozac, Sarafem, Celexa, Paxil, Brisdelle, Pexeva, Lexapro, Luvox, Viibryd)
- [ ] Anti-anxiety medication (e.g. Alzam, Azor, Xanax, Zopax, Lexotan)
- [ ] Allergy medication (e.g. antihistamines)
- [ ] Blood pressure medication
- [ ] Other (Please specify)