Post-Covid: Exploring Fluctuations and Associations of Physical Fatigue and Depressive Mood in Dutch Patients – An N-of-1 study.

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Abstract

Background: Many individuals still suffer from post-Covid, a quite novel chronic disease with symptoms such as fatigue and mood disturbances. Previous studies found fluctuations and positive associations between physical fatigue and depressive mood in groups with other chronic diseases. Since the experience of the individual is mostly unknown, this study investigates the fluctuations and association of physical fatigue and depressive mood in post-Covid patients on an individual level over time.

Method: This studies N-of-1 design focused on individuals of a sample consisting of 5 Dutch patients (M_{age} = 57.80, SD_{age} = 6.08, 60% male). For each individual, fluctuations in physical fatigue and depressive mood were investigated using graphs. To analyse the prediction of depressive mood by physical fatigue a dynamic regression model was used.

Results: While the whole sample displayed high levels of physical fatigue (M=5.07, SD=1.65) and medium levels of depressive mood (M=3.47, SD=2.18), fluctuations in both variables differed unambiguously between all participants. Some showed large fluctuations in physical fatigue, but not depressive mood. Others displayed the opposite or only small fluctuations in both variables. Furthermore, physical fatigue did not predict depressive mood within the individual over time.

Conclusion: The results of this study are partially in line with previous research. The fluctuations of physical fatigue and depressive mood are so individual, that no general conclusion can be drawn. Contrary to research on a group level, this study shows no association on an individual level. These results highlight the importance of individual assessment and treatment options for POC-patients.

Keywords: Post-Covid, physical fatigue, mood, N-of-1, experience sampling

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Introduction

1.1 Post-Covid

In 2019 the world was brought to a hold by SARS-COV-2. While millions of people have lost their lives, many still struggle with the aftermath the virus has caused. Approximately, 10 – 20% of people suffer from what can be called “post covid syndrome” (PCS) (World Health Organization [WHO], 2021). Other terms are “post-acute sequelae of SARS-CoV-2 infection” (PASC), “long-COVID-19”, and “post-acute COVID-19” (Lopez-Leon et al., 2021). Within approximately 3 months after the initial infection individuals show symptoms, such as shortness of breath, which last for at least 2 months and cannot be explained by any other diagnosis (World Health Organization [WHO], 2021). These symptoms could either remain from the acute infection or be newly developed, independent of the infection’s severity (Lopez-Leon et al., 2021; World Health Organization [WHO], 2021). As seen in Figure 1, one of the most common post-covid symptoms reported is fatigue, but also the psychological well-being of patients seems to be affected (Hellwig & Domschke, 2022; Joli et al., 2022; Li et al., 2022; Lopez-Leon et al., 2021). Especially tendencies of anxiety and mood disorders can be observed in some post-Covid patients (Hellwig & Domschke, 2022; Joli et al., 2022; Lopez-Leon et al., 2021).

Looking at research on other diseases, such as multiple sclerosis or cancer, correlations between these two symptoms, fatigue and mood (disorders), have been found (Broeckel et al., 1998; Kroencke et al., 2000). However, in the context of Post-Covid this association is vaguely researched until now. In order to develop as specific as possible interventions for post-Covid patients at a later point in time, it is of interest to research symptoms on an individual state level over a longer period. This might help to elaborate what the relationship between fatigue and mood looks like and to intervene at the right moment. Therefore, this study will focus on fatigue and depressive mood as well as their association over time in post-covid patients.

1.2 Fatigue

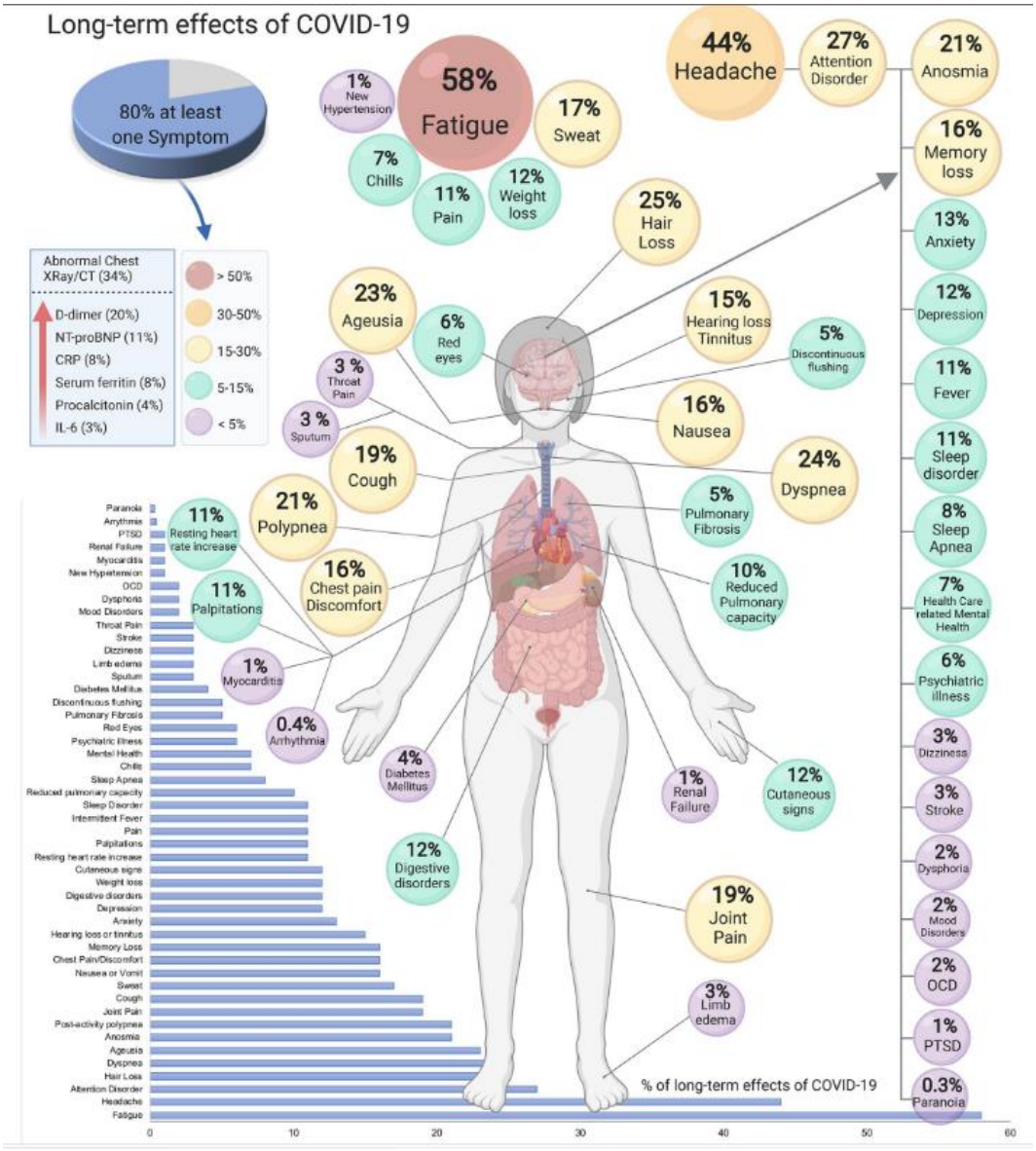
Fatigue is a complex phenomenon which commonly occurs in individuals with acute and chronic medical conditions, such as cancer or post-viral infections, but also in healthy individuals (Billones et al., 2021). Many see fatigue as a multidimensional construct, but there is no universal definition (Norton et al., 2015; Pattyn et al., 2018). Appendix A shows a list of several definitions of fatigue as found in literature. Based on this list of definitions, in this study fatigue is defined as severe and persistent exhaustion, tiredness and weakness which manifests itself in cognitive or physical form. Mental fatigue manifests itself by the subjective effort an individual has to put in paying attention, since cognitive functions such as attention and

concentration can be diminished (Lou, 2009). On the other side, physical fatigue is illustrated by the subjective effort an individual has while e.g. walking, engaging in manual labour or anything that requires muscle force (Lou, 2009). Since fatigue is not quickly relieved by resting, it is often perceived as life altering and lowering quality of life.

Until now, little is known about the course of fatigue in post-Covid patients. However, in several studies patients with multiple sclerosis (MS), spinal cord injuries (SCI) or cancer display fluctuations of fatigue on a long-term, as well as daily level (Badr et al., 2006; Kuzu et al., 2022; Powell et al., 2017; Veldhuijzen van Zanten et al., 2021). For example, Badr et al. (2006) found fatigue to vary during the day with higher scores in the afternoon and evening in breast cancer patients. Moreover, fatigue showed higher moment to moment fluctuations, than day to day changes, with a peak during the afternoon in MS patients (Powell et al., 2017). Besides, Powell et al. (2017) attributed approx. 50% of the variability in fatigue severity to individual differences. This indicates fatigue should be observed on an individual and state level. Because it is unclear until now if these moment-to-moment fluctuations reported in e.g. MS patients hold true in individuals with PCS.

Due to the overwhelming lack of e.g. energy and concentration, the individuals concerned might experience changes in mood or even develop comorbidities, due to a feeling of guilt and their current incapability (Lasseter, 2009). For example, an anxiety disorder or a depression, which is similar to what post-covid patients seem to experience (Hellwig & Domschke, 2022; Norton et al., 2015).

Figure 1 Quantity of post covid symptoms in percentages found in meta-analysis.. (Lopez-Leon et al., 2021).



1.3 Mood

Mood is an unfocused affective state, which is ever-present and moulding moment to moment experiences (Lischetzke, 2014). A distinction between trait and state mood can be made. Meaning, state mood fluctuates around a certain degree of a baseline mood, which is different for everyone. It "reflects the effects of a situation and the interaction between person and situation" (p. 4116, Lischetzke, 2014).

Similar to fatigue, low or depressive mood is a symptom apparent in post-covid and several other chronic diseases, such as cancer and MS (Lopez-Leon et al., 2021; Powell et al., 2017; Valentine & Meyers, 2001; Visser & Smets, 1998). Comparable to fatigue, mood was also found to be varying in patients with chronic diseases such as cancer and Parkinson (Badr

et al., 2006; Richard et al., 2001). These fluctuations seem to be quite different in each individual, with them experiencing highs and lows in mood at different times of the day (Richard et al., 2001). In contrast, Kratz et al. (2017) observed less variation and rather stable depressive mood within MS patients. As both constructs, fatigue and mood are varying an association between these two variables was found in other chronic diseases. However, it is yet unclear if this holds true within post-covid patients.

1.4 Associations between Fatigue and Mood

As mentioned above fatigue and depressive mood have been found to be associated in previous research on post-Covid and chronic diseases (Kentson et al., 2016; Ma et al., 2021; Townsend et al., 2020). Moreover, Ford et al. (1998) acquired results of a positive relationship between fatigue and depressive mood in individuals with MS. This association was not only found in cross-sectional studies, but also observed in a longitudinal study of patients with MS by Veldhuijzen van Zanten et al. (2021). They concluded that higher levels of fatigue are associated with higher levels of depressive mood (Hospital Anxiety and Depression Scale (HADS) scores). Moreover, the physical aspects of fatigue seem to have a stronger association to depressive mood than the mental aspects (Veldhuijzen van Zanten et al., 2021). Therefore, the focus of this study will lie on physical fatigue.

1.5 This Study

To summarize, post-Covid is a relatively new and unknown field of research with fatigue as one of the most common symptoms individuals are experiencing. Fatigue seems to increase the risk of experiencing mood disturbances. Both, fatigue and depressive mood, appear to be experienced quite varying, personal, and to lead to a lower quality of life in patients with chronic diseases (Gullo et al., 2019; Visser & Smets, 1998; Waldheim et al., 2013). Therefore, it is of interest to take a closer look at the experience of fatigue and depressive mood in post-covid patients and see if they have similar experiences as individuals with other chronic diseases. Since most studies above have been focusing on the association between fatigue and depressive mood on a cross-sectional group level, it is still uncertain whether this relationship holds true in post-Covid patients and on a predictive, daily and individual level. Especially, since both variables, fatigue and (depressive) mood, have been proven to vary. Besides, the cross-sectional approach on a group level potentially misses certain patterns within individuals leading to unspecific interventions. However, different people might have different experiences. Thus, this study aims to provide new insights about the fluctuations and the relationship between physical fatigue and depressive mood in post-COVID patients, while focusing on a daily within person level. The N-of-1 approach facilitates, the gathering of

individual experiences which can get lost in larger scale research. Besides, the N-of-1 approach gives the opportunity to see characteristics of patients, which might influence how the symptoms are experienced. Furthermore, the closer the focus is on the within person level, the better interventions could be adapted to the individual at a later point in time (McDonald et al., 2020). For example, fitting to the patients age, gender and especially the varying symptoms. Thus, the main goal of this paper is to gather new insights on fluctuations of physical fatigue and depressed mood, as well as their potential association within post-Covid patients.

1. ***In how far does physical fatigue fluctuate within the individual throughout the days?***

   1.a Which differences in the level of physical fatigue fluctuations can be observed between individuals?

2. ***In how far does depressive mood) fluctuate within the individual throughout the days?***

   2a. Which differences in the level of depressive mood fluctuations can be observed between individuals?

3. ***Does physical fatigue predict low/depressive mood within the individual throughout the day?***

2. Method

The current study is following a N-of-1 design, meaning each individual will serve as a subject to the analysis separately. Within this project the data from an experience sampling method (ESM) study by Wensink et al. (2023) is used. This ESM study was a supplementary study to a longitudinal cohort study on health after Covid-19 hospital discharge from the MST hospital in Enschede.

2.1 Participants

For the ESM study, participants were purposively selected from the cohort project. Ex-patients were asked to fill out surveys directly at discharge (baseline), three months, six months, nine months, and twelve months after hospital discharge. During the longitudinal study, interviews were conducted with participants who stated they felt significantly worse one year after discharge (n = 16) and those who stated to feel significantly better (n = 8). During the interview study these 16 participants who's health had deteriorated, were invited to take part in the ESM study. However, only 11 individuals enrolled. These 11 participants, which were included, met the following criteria: They a) were discharged from hospital after a PCR confirmed Covid-19 infection b) were impacted by symptoms attributed to the lack of a

recovery c) were in possession of a smartphone d) were at least 18 years old e) were proficient in Dutch and f) gave consent before participating. For the current study an additional criterion was needed to secure sufficient data for an analysis on an individual level. Therefore, all participants with more than 50% of missing data regarding physical fatigue and depressive mood, were excluded. Subsequently the participant number for the current study is $n = 5$.

Table 1 Demographic data per participant

Participants	**(1)**	**(2)**	**(3)**	**(4)**	**(5)**
Age	48	60	62	54	65
Gender	female	male	male	male	female
Comorbidity	none	depression	other	none	other
BMI[a]	39.44	24.93	41.77	29.24	25.59

Note: [a]Body Mass Index < 18.5 = underweight; ≥ 18.5 = healthy weight; ≥ 25.0 = overweight; ≥ 30.0 = obesity

As seen in Table 1, the remaining five participants were between 48 to 65 years old *(M*=57.80, *SD*=6.08) and mainly males (60%, *n*=3). Furthermore, 60% (*n*=3) indicated they suffer from comorbidities such as depression. Additionally, four participants were overweight (BMI > 25), with one of them being obese (BMI > 30).

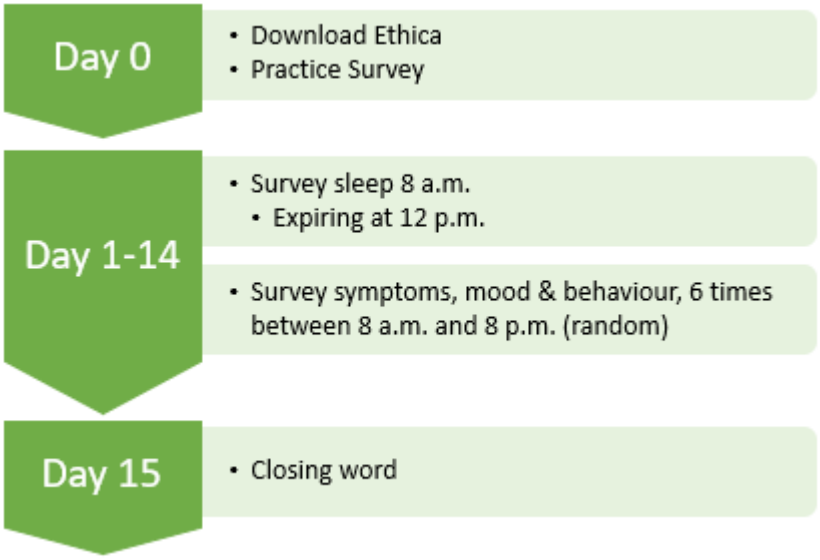
2.2 Design & Procedure

The Ethical Committee of the Behavioural Sciences faculty of the University of Twente (210799) and the Medisch Spectrum Twente (K20-30) granted approval in May 2021. The data collection itself took place between September 5th and November 27th, 2021.

For designing the ESM study guidelines by Conner and Lehman (2012) were taken into consideration. Thus, the data collection lasted for 14 consecutive days and an additional practice and end day. This duration was decided on as previous studies showed a timespan of at least one week up to a maximum of two weeks produces the most representative data, before the quality tends to decline (Hektner et al., 2007; Stone et al., 1991; van Berkel et al., 2017). The participants were provided with the surveys via the smartphone application Ethica. In order to eliminate malfunctions, the Ethica surveys were pilot-tested amongst the researchers and a student with long-Covid symptoms. Afterwards, issues that have risen were fixed. During the interview the participants were asked to join the ESM study, which they started directly afterwards. Within the Ethica application an informed consent had to be signed, before starting with the surveys and on the first day a practice survey was sent out, which was identical to the actual survey. Similar to other ESM studies the signal-contingent semi-random sampling strategy was used to ask participants about their mood and behaviour (Wheeler & Reis, 1991).

Questionnaires were sent six times a day within random two-hour timespans between 8 a.m. and 8 p.m.. Meaning 6 notifications for survey were sent, starting between 8 a.m. and 10 a.m. until the last notification between 6 p.m. and 8 p.m. (see Figure 2). Since there is a high probability for people to interact with the application within five minutes after the notification, an expiration time of 15 minutes was set (van Berkel et al., 2017). Wensink et al. (2023) decided on six measurement points throughout the day, because the optimum is said to lie between five and eight measurements.

Figure 2 Overview of the ESM study design.



2.3 Materials

The ESM study used the design- and application platform Ethica, which participants installed on their smartphones. The app presented the participants with three different surveys. A practice survey, which was identical to the actual survey and two state surveys. One concerning previous night's sleep and one other survey concerning momentary symptoms, mood and behaviour. Only the latter is used within this study (Appendix B) and consisted of 21 questions about momentary states, such as fatigue and depressive mood e.g. feeling sad or gloomy. Fatigue was measured on a 7-point Likert scale ranging from (1) *strongly disagree* to (7) *strongly agree* using an item based on the Patients-Health-Questionnaire-9 (PHQ-9) (e.g. 'Right now, I feel physically tired.') (Kroenke et al., 2001). Similarly, depressive mood was measured on a 7-point Likert scale ranging from (1) *strongly disagree* to (7) *strongly agree* with an item based on the Hamilton-Rating-Scale-for-Depression (HRSD-NL) (e.g. 'Right now, I feel down.') (Hamilton, 1986).

2.4 Data Analysis

To analyse the collected data IBM SPSS Statistics 28 was used. The received dataset was in long format and Dutch. Therefore, the variables were translated into English. Since missing data can bias the statistical outcome of the analysis a missing value analysis was conducted. According to McDonald et al. (2020) a basic imputation, such as using the mean or median of surrounding data points, would be enough for missing data < 10%. However, if more data is missing multiple imputations are needed. Participants of this study missed more than 10% of the data. When taking a closer look, values were missing mostly due to participants missing complete questionnaires at various points. Unfortunately, multiple imputation was not possible because mostly complete questionnaires at timepoints were missing. Moreover, the tool in SPSS to perform multiple imputations with data in long format was not available. Thus, all participants with more than 50% missing data of either fatigue or depressive mood were excluded from further analysis. Leading to the 5 participants being included.

After excluding the participants, the SPSS outcome was split per participant. Then depressive mood and physical fatigue were visualised by plotting them over all 84 timepoints for each participant. This way, the level and fluctuations of physical fatigue and depressive mood throughout the studies duration were displayed. For example, both variables fluctuating in a similar shape and at a similar time, or one increasing while the other one is decreasing.

In order to answer the research questions a dynamic regression analysis was performed separately for each participant. All statistical properties (e.g. mean, variance and autocorrelation) should be approximately stationary for the outcome variable (McDonald et al., 2020). Therefore, stationarity was assessed by creating two partition variables of equal size for depressive mood, calculating their descriptive statistics and evaluating if there is a considerable change over time (McDonald et al., 2020).

Furthermore, periodicity was analysed by using time variables day of the week and measurement timepoints (1-84 timepoints) as predictor, and depressive mood as dependent variable in a linear regression. If the 95% confidence interval of the predictor included zero, there was no periodicity and thus no time pattern present (McDonald et al., 2020).

Another important aspect to consider when working with time-series data, is autocorrelation. To test for autocorrelation (AC) in the outcome variable depressive mood, autocorrelograms were constructed. If a significant AC was identified the partial autocorrelation function served as an indicator on the order of autocorrelation (e.g. first order = current observation is dependent on the last timepoint approx. 2 hours ago; second order = current observation is dependent on the observation previous to the last approx. 4 hours ago, etc.)

(Quinn et al., 2013). If autocorrelation was present, the variables were lagged and included into the regression model to account for the autocorrelation.

Lastly, a regression analysis was conducted in which it was suggested that depressive mood was predicted by physical fatigue at a former timepoint. The variable depressive mood was chosen as dependent variable (DV), while physical fatigue (lag 1), was used as independent variable (IV). To account for autocorrelation in the dependent variable depressive mood lag 1 and/or 2 were added as IVs, depending on the outcome of the autocorrelograms. Considering periodicity, the variables which displayed time trends were added to the model of the respective participant as independent variables.

3. Results

After checking the dataset, it became apparent, that five participants were missing more than 50% of the data needed for this analysis. The remaining five were included in the analysis. However, they also showcased large amounts of missing data for physical fatigue and depressive mood, ranging from 9.5% to 28.6% (see Table 2).

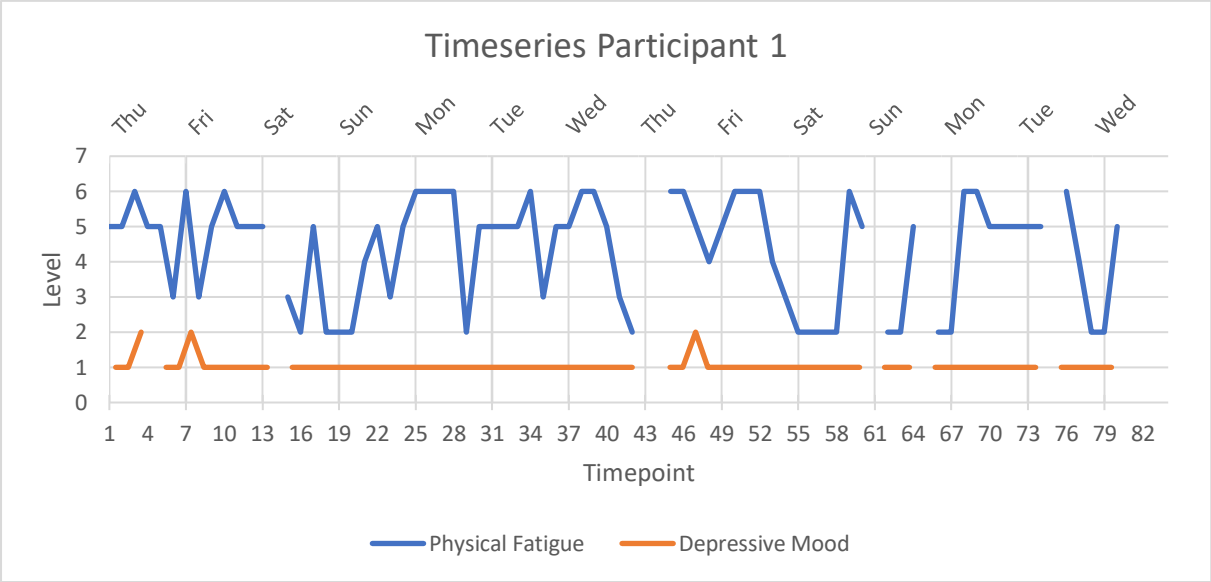
Throughout the whole sample, levels of physical fatigue ranged from 2 to 7 with an average of 5.07 (*SD*=1.65), while depressive mood ranged from 1 to 7 with an average of 3.47 (*SD*=2.18). Further, Table 2 displays the mean of each participant.

Table 2 Descriptive statistics physical fatigue and gloominess and their missing data per participant

	Physical fatigue			**Depressive mood**		
Participants	**Mean**	**SD**	**Missing (%)**	**Mean**	**SD**	**Missing (%)**
(1)	4.36	1.50	11.9	1.04	0.20	13.1
(2)	6.90	0.30	27.4	6.48	0.54	28.6
(3)	4.76	1.32	9.5	2.67	1.15	9.5
(4)	3.56	1.41	26.2	2.23	0.61	26.2
(5)	6.00	0.84	27.4	5.68	0.54	28.6

Participant (1)

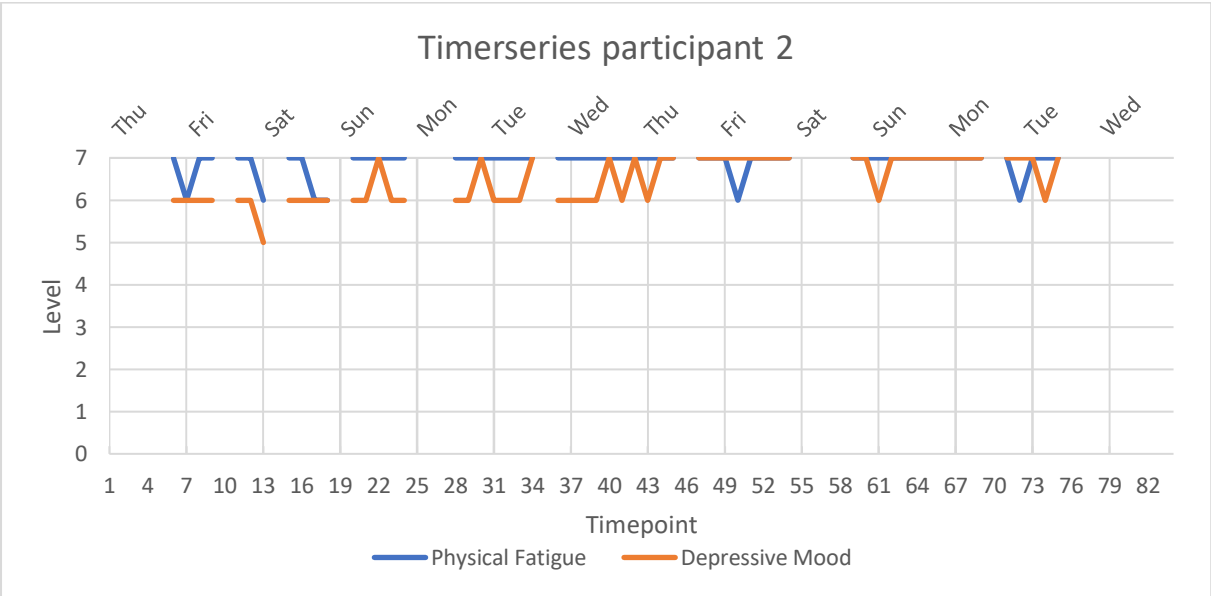
Figure 3 Physical fatigue and depressive mood over all timepoints for participant 1.



As seen in Figure 3 and Table 2, participant 1 showed large variation in physical fatigue of the participants in the sample, with scores ranging from 2 to 6. In contrast depressive mood was mostly stable around 1 with three peaks at 2. Thus, the participant experienced rather high physical fatigue (M=4.36, SD = 1.50) and low depressed mood (M = 1.04, SD = 0.20). Figure 3 clearly displays no relationship between physical fatigue and depressive mood. Therefore, no further analysis was conducted.

Participant (2)

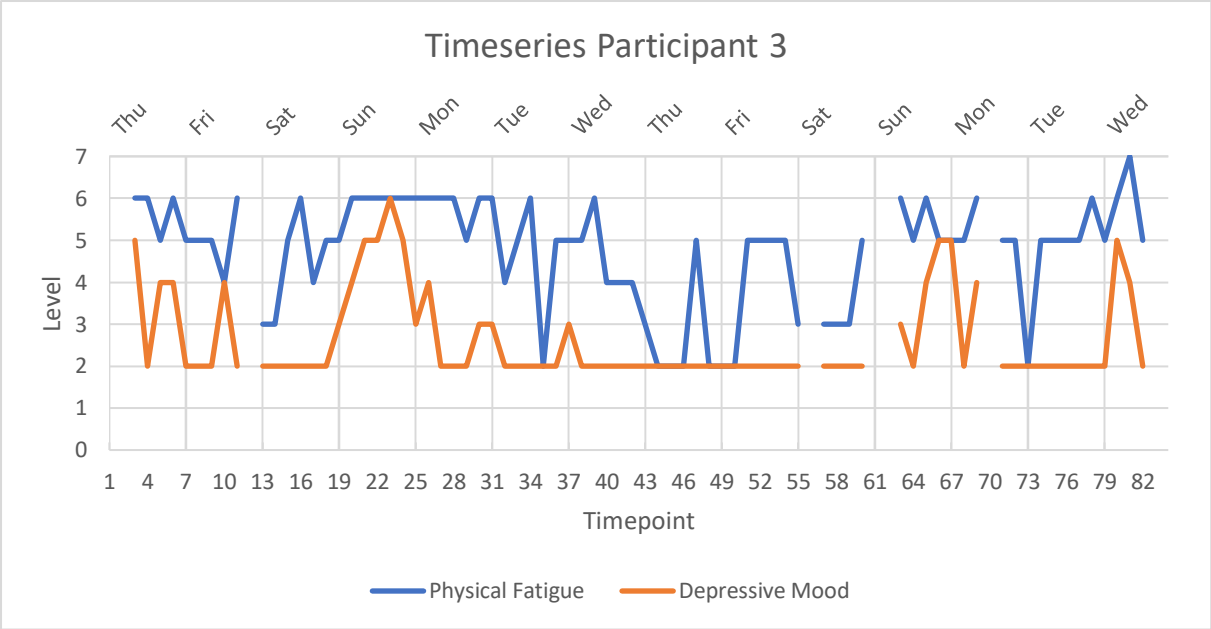
Figure 4 Physical fatigue and depressive mood over all timepoints for participant 2.



Participant 2 experienced very little to no variation in physical fatigue and depressive mood (Figure 4). Physical fatigue ranged from 6 to 7 (M = 6.90, SD = 0.30) and depressive mood ranged from 5 to 7 (M = 6.48, SD = 0.54). Thus, out of the sample participant 2 experienced the highest levels of fatigue and depressive mood. Important to mention is that this participant was the only one suffering from a depression as well. Since, there is very little to no variation in the scores no further analysis was conducted.

Participant (3)

Figure 5 Physical fatigue and depressive mood over all timepoints for participant 3.



Like participant 1, participant 3 experienced large variations in physical fatigue ranging from 2 to 7. Additionally, this participant displayed the largest variations in depressive mood compared to the other participants in the sample, ranging from 2 to 6. Looking at Figure 5 and Table 2 physical fatigue scores seem to have gathered at the mid to higher end of the scale with a M = 4.76 (SD = 1.32), while depressive mood was general rather low, with M = 2.67 (SD = 1.15). Since there was a large variation in both variables the analysis was continued. Autocorrelation was adequately specified at lag 1 for depressive mood (Appendix C). Furthermore, the day in the week displayed periodicity since the 95% CI did not include 0 (95% CI: -0,359, -0.117) (Appendix C). To account for this time trend, this variable was included in the model as additional IV. Looking at the results of the dynamic regression analysis (see Table 3) it becomes clear, that an increase in physical fatigue was not a significant predictor (95% CI: -0.156, 0.215) of depressive mood over all time points (B = 0.03, SE = 0.09) in this individual.

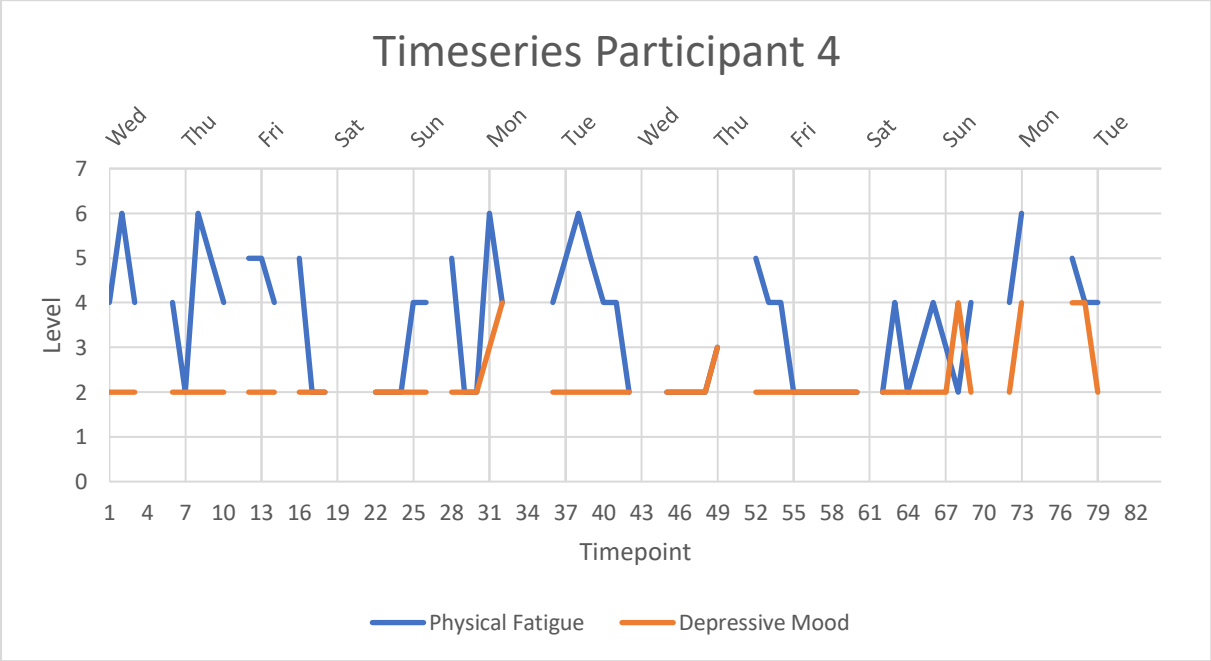
Table 3 Results of dynamic regression analysis for Participant 3

	Unstandardized					95% CI for B	
	B	**Std. Error**	**β**	**t**	**Sig.**	**Lower Bound**	**Upper Bound**
(Constant)[a]	2.176	.611		3.561	<.001	.956	3.395
Physical fatigue lag 1	.030	.093	.036	.319	.751	-.156	.215
Depressive mood lag 1	.383	.109	.391	3.517	<.001	.166	.601
Day in the week	-.179	.061	-.326	2.915	.005	-.302	-.056

[a] Dependent variable: depressive mood

Participant (4)

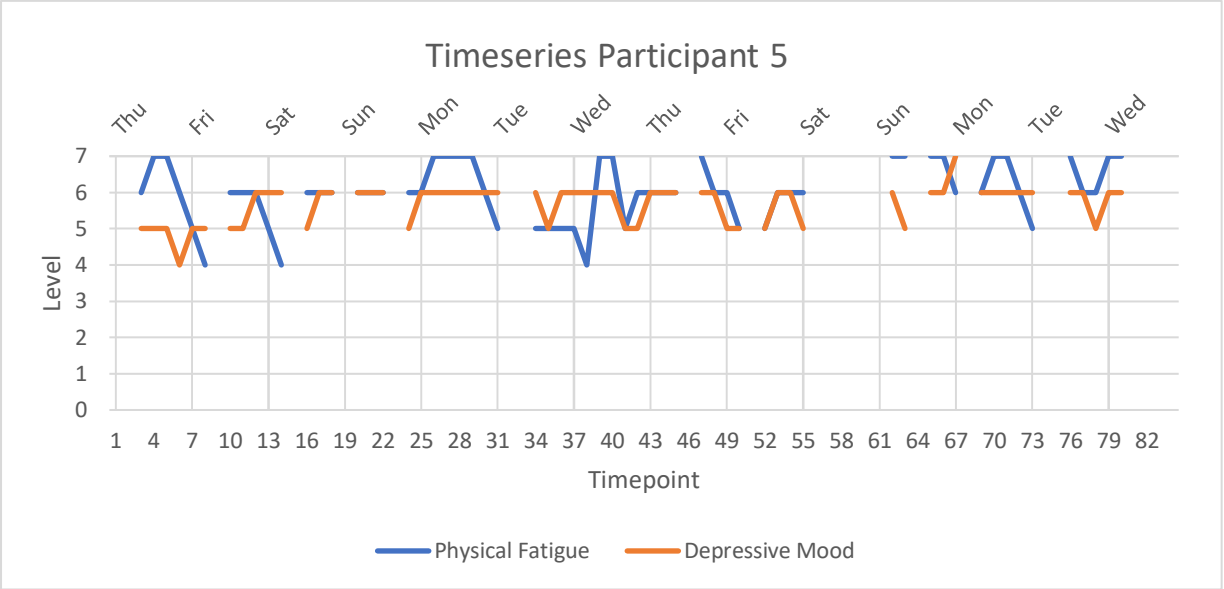
Figure 6 Physical fatigue and depressive mood over all timepoints for participant 4.



Looking at Figure 6, physical fatigue was varying largely between level 2 and 6, while depressive mood was rather stable at level 2 with four peaks at level 4. Compared to the other participants the general level of physical fatigue was on the lower part of the scale with M = 3.56 (SD = 1.14). Similarly, participant 4 scored second lowest of the sample in the average depressive mood (M = 2.23, SD = 0.61). Since there was not much variation in depressive mood, no further analysis was conducted.

Participant (5)

Figure 7 Physical fatigue and gloominess over all timepoints for participant 5.



As summarized in Table 2, participant 5 displayed the second highest scores in physical fatigue ranging from 4 to 7 with M = 6.00 (SD = 0.84). Similarly, depressive mood scores ranged from level 4 to 7 (M = 5.68, SD = 0.54), while rather gathering on the upper end of the scale (see Table 2). Since the participant was missing appox. 28% of the data, it was difficult to identify a pattern. However, due to the fluctuations in both variables further analysis was conducted. Furthermore, autocorrelation was specified at lag 1 for depressive mood (Appendix D). For this participant periodicity at the level of the general timepoint (95% CI: 0.002, 0.014), day of measurement (95% CI: 0.016, 0.084) and day in the week (95% CI: -0.161, -0.026), was found (Appendix D). Therefore, these variables were included as IVs in the dynamic regression model. The result of the dynamic regression analysis (see Table 4) indicates that an increase in physical fatigue is not a significant predictor (95% CI: -0.287, 0.1196) of an increase in depressive mood throughout the days (B = - 0.046, SE = 0.119) in this individual.

Table 4 Results of dynamic regression analysis for Participant 5

	Unstandardized					95% CI for B	
	B	**Std. Error**	**β**	**t**	**Sig.**	**Lower Bound**	**Upper Bound**
(Constant)[a]	5.814	.875		6.648	<.001	4.032	7.595
Physical fatigue lag 1	-.046	.119	-.072	-.385	.703	-.287	.196
Timepoint	-.033	.061	-1.395	-.535	.597	-.157	.092
Day	.229	.367	1.626	.624	.537	-.518	.976
Day in the week	-.034	.054	-.122	-.637	.528	-.144	.075

[a] Dependent variable: depressive mood

4. Discussion

4.1 Main findings

This study focused on investigating fluctuation of physical fatigue and depressive mood, as well as their potential association in patients suffering from post-COVID. The fluctuations in physical fatigue and depressive mood differed unambiguously between all five participants during the days. Indicating that the experience of both is a very individual experience, different in intensity and variation. Within this sample more fluctuations were seen in physical fatigue compared to depressive mood (Figure 3-7). Furthermore, within no participant physical fatigue predicted depressive mood over time. In contrast to expectations and previous research, this association did not hold true on an individual level in PCS patients. Although, it is difficult to compare the previous, mostly cross-sectional, research with the current N-of-1 study, the following will do.

Regarding research question one, results show that the participants experienced medium to high levels of physical fatigue, which is reflective of previous findings of fatigue being one of the most prominent symptoms of post-COVID (Joli et al., 2022; Lopez-Leon et al., 2021). These results are also in line with the medium to high levels of fatigue found in MS and cancer patients (Badr et al., 2006; Powell et al., 2017; Veldhuijzen van Zanten et al., 2021). While Badr et al. (2006) and Powell et al. (2017) observed fatigue over a longer period with multiple measurements per day, similar to the current study, Veldhuijzen van Zanten et al. (2021) conducted a longitudinal study of 7 years with only one measurement of fatigue per year. Different to the current study is that all three researchers did not differentiate between physical and mental fatigue but focused on general fatigue. Although, the general experience of physical

fatigue was rather high in the current sample, variations within most individuals could be observed. Large variations were especially seen in participant 1 and 3. In contrast to the MS and breast cancer patients peaking in the afternoon (Badr et al., 2006; Powell et al., 2017), participant 1 usually had peaks of physical fatigue in the first half of the day with a little lower level on the weekend. In line with that, participant 4 peaked mostly during the first half of the day and sometimes in the evening as well. The latter was also present in the breast cancer patients studied by Badr et al. (2006). Furthermore, the fatigue of participant 5 peaked during the midday and stayed constant for a few hours before declining in the afternoon. Participant 2 had even more different fluctuation pattern, displaying rather constant levels not comparable to previous research. Thus, the fluctuations of physical fatigue were all distinct from each other and in contrast to the development it showed on a group level in other chronic diseases.

For research question two results indicate the sample experienced depressive mood on a moderate level but in its whole range, from low levels to high levels; showing definite differences between the participants. However, there was not much variety within the individual. The visualisation showed in participants 1 and 2 there is little to no change in the level of depressive mood. Similarly, participant 4 displayed a quite constant level, while participant 3 experienced a large variety, especially in week 1. Participant 5 could be positioned somewhere between these two, because she displays a few more changes than participant 1, 2 and 4, but on a smaller range than participant 3. These findings are partially in line with the research mentioned above which suggested mood to be varying over time (Badr et al., 2006; Richard et al., 2001). However, Richard et al. (2001) findings also display the different mood experiences individuals with Parkinson had throughout the day. While the mood of some varied a lot during the day, others experienced rather stable moderate levels similar to the participants in the current study. Important to mention is, that Badr et al. (2006) focused on the samples average mood throughout the day and not the individuals. Moreover, only Kratz et al. (2017) focused specifically on depressed mood in MS patients. They displayed one example patient who exhibited rather stable and low within person depressed mood throughout the studies duration, similar looking to participant 1. Displaying low and stable levels of depressed mood, but varying levels of fatigue. In contrast, an explanation for participant 2 stable and high scores could be the comorbid depression he is suffering from, because Cowdry et al. (1991) found that people with a major depression displayed low variability in their mood scores. Furthermore, Townsend et al. (2020) suggested, that a predisposing factor for fatigue is a depressive disorder. This might explain the extremely high and stable fatigue scores, compared to the other participants.

Although, there might be an association between physical fatigue and depressed mood in some individuals, in none of the post-COVID participants was depressive mood predicted by physical fatigue from a former timepoint. This is partially in line with the outcome cancer patients displayed in Visser and Smets (1998) research. In their longitudinal study over approx. 9.5 months they concluded that fatigue and depression did not follow the same course over time and fatigue only showed low predictive power. For participants 3 and 5 the further analysis resulted in a similar outcome, with no prediction of depressive mood by physical fatigue. It is difficult to compare previous research to the current study since they focused on the association between fatigue and depressive mood on a group level, not individual level. This might be a reason why several study-outcomes were positive associations between fatigue and mood in chronic diseases such as MS, cancer and COPD, but not for the current study (Badr et al., 2006; Kentson et al., 2016; Veldhuijzen van Zanten et al., 2021). Furthermore, not all preceding studies differentiated between total, mental and physical fatigue. Important to mention is that, while Veldhuijzen van Zanten et al. (2021) found a stronger association between physical fatigue and mood, than mental fatigue and mood, Ford et al. (1998) discovered no correlation between physical fatigue and mood. Concludingly, while an association between (physical) fatigue and (depressed) mood holds true on a cross sectional group-level in several chronic diseases, physical fatigue did not predict depressive mood in individuals with PCS over time. This highlights the complexity of this relationship, which needs further thorough investigation. Other factors, such as social support or the activity a person engages in might influence said relationship and should potentially be considered during assessment and treatment of post-Covid syndrome.

4.2 Limitations & Strengths

Even though not all findings are in line with previous research, this study holds some advantages compared to others. Besides the fact that it focuses on patients suffering from post-COVID, a new chronic disease, the largest advantage is the N-of-1 approach. By using the N-of-1 approach the focus lies on the individual experience compared to a group-level analysis. This allows to test theory on a within person level, which has been supported at a group level. Furthermore, differences between patients become apparent and can be taken into consideration when developing treatments in the future. As Kwasnicka and Naughton (2019) mentioned, it gives the opportunity to make personalized recommendations. So, no patient gets lost within a group, potentially leading to their unsuccessful treatment in the future.

Furthermore, using ESM as a form of data collection provides a large amount and detailed form of momentary data. Furthermore, recall bias is reduced as participants are asked

about their symptoms in real-time, while increasing ecological validity (Conner & Lehman, 2012; Larson & Csikszentmihalyi, 2014; Napa Scollon et al., 2009). The N-of-1 approach then offers the opportunity to investigate dynamic relationships on this moment-to-moment base. Furthermore, this study is followed the guidelines for a N-of-1 Design by McDonald et al. (2020) ensuring a well-founded implementation.

Nonetheless, the study has some limitations. Namely, the small sample size of N-of-1 studies, which prevents generalization of the results found within these participants since they are specific to the person. Besides, the sample was quite homogenous, which prevented the option to e.g. look at younger patients' experiences. Furthermore, the most limiting factor within this study was the data quality. Sadly, many participants had to be excluded due to large amounts of missing data and even the ones included still missed quite a lot of measurement points. This might be the result of the ESM study from which the data was utilized. Although the number of measurements scheduled was according to other ESM studies, the burden of six prompts per day might have been too much for some participants, leading them to skipped surveys and missing data (Eisele et al., 2022; Hektner et al., 2007; Stone et al., 1991). Considering the persons of interest, it might be that for some individuals the participation was sheer too much of an effort, regarding their level of energy/fatigue or concentration. While just using a single item to measure physical fatigue might diminish validity, several ESM studies used the PHQ-9 item before and were able to provide good pictures of daily fluctuations (Brys et al., 2020; Lenaert et al., 2020; Lenaert et al., 2022). However, only a specific group of participants was included in this study, hindering the generalizability of the results, which are specific to these five individuals. Furthermore, no sensitivity analysis as conducted leaving it unclear how stable the results are. While the study provided insights into the individual fluctuations of physical fatigue and depressive mood it is still unclear what causes or facilitates these fluctuations. Leaving the opportunity for further research.

4.3 Further Research

Since this is the first known study to investigate the fluctuations and predictive nature of physical fatigue and depressive mood in post-COVID patients, replications should take place to further confirm or deny the results. This way the outcome, that individuals experiencing physical fatigue and depressive mood different from each other, could be further validated. The same applies to the not identified prediction of depressive mood by physical fatigue from a former timepoint. Since the experience of the participants seems so individual, it might be that in e.g. younger patients this prediction holds true. Thus, a wider range of participants would be advisable. As mentioned above, further insights into the cause of the fluctuations in physical

fatigue and depressive mood could be of interest too. Interesting to know would be which activities participants engaged in as the fluctuations occur and are they potentially predicting these fluctuations. Since affective states, such as depressed mood are influenced by the persons surroundings it might be, that depressive mood is affected by the activity the person engaged in as well. This additional information might serve as a basis for behavioural adjustments PCS patients could use to reduce their suffering.

5. Conclusion

All together this study provided a first glance into the individuals experience of physical fatigue and depressed mood over time in post-COVID patients. In contrast to physical fatigue, which was fluctuating to a high degree in most individuals, depressive mood seemed more stable with mostly small variation. However, the experience of both constructs was different in each person, indicating that no general conclusion in regard to fluctuations of physical fatigue and depressive mood can be drawn. Furthermore, this study stands in contrast with previous research of fatigue and mood in other chronic diseases. While associations between the two variables have been found in other chronic diseases before, they hold not true on an individual level in post-COVID patients. Since this study is the first known to focus on the individual level of participants regarding this topic, the comparison with cross-sectional results is partially difficult. It could be that simply no association between the specific variables physical fatigue and depressed mood exist or that this relationship is just not present on an individual level. The most important outcome seems to be that different people experience physical fatigue and depressive mood differently, highlighting the importance of individual treatment options. Furthermore, the fluctuations of symptoms should already be considered during the assessment phase and diagnostics. Further research regarding the context patients were in and potential predictors of the fluctuations could bring more information relevant for future treatment development. This could be step towards a more client centred care.

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Appendix

Appendix A summary of definitions of fatigue by Billones et al. (2021)

Definitions of fatigue from non-oncologic medical conditions.

Medical Condition	Definition of Fatigue	References
Autoimmune Rheumatic Disease	".. persistent, and severity is similar to the chronic fatigue syndrome … fatigue generally is subscribed to disease-related factors, especially inflammation, anemia and pain."	van Hoogmoed et al. (2010)
Chronic Obstructive Pulmonary Disorder (COPD)	"… described mostly in relationship with muscular force exhaustion as if following a strenuous exercise period and with no malaise."	Antoniu & Ungureanu (2015)
Cushing's Syndrome	"Mental fatigue is characterized by a mental exhaustion which appears especially during sensory stimulation or following mentally strenuous tasks. Other typical features are the long recovery time that is needed for restoration of mental energy, irritability, impaired memory, and concentration as well as stress, sound, and light hypersensitivity."	Papakokkinou et al. (2015)
Epilepsy	"… extreme and persistent tiredness, weakness or exhaustion that could be mental, physical or both."	Hernandez-Ronquillo et al. (2011)
Fibromyalgia	"… disruptive or extremely disruptive" to health-related quality of life.	Li et al. (2017)
	"… profound and overwhelming, more severe, constant, and unpredictable than normal tiredness, not relieved by resting or sleep, not proportional to effort exerted, and disruptive in terms of motivation, activities, and cognition."	Kratz et al. (2016)
Inflammatory Bowel Disease	"… unpleasant, multifactorial and multifaceted symptom that is strongly associated with depression and poor quality of life (QoL). … a sense of continuing tiredness, with periods of sudden and overwhelming lack of energy or feeling of exhaustion that is not relieved, or fully relieved following rest or sleep."	Norton et al. (2015)
Multiple Sclerosis	"… most common, debilitating and life altering symptoms."	Learmonth et al. (2013)
Myasthenia Gravis	"… a complex phenomenon and includes both physiological and psychological factors, a distinction has recently been made between fatigue as a subjective feeling of tiredness, lack of energy, and difficulty concentrating, and muscle fatigability defined as the difficulty initiating or sustaining muscle activities."	Elsais et al. (2013)
Parkinson's Disease	"… an important and frequent non-motor symptom. It is difficult to describe, there are no biological markers, being always a subjective definition. It is described with a wide range of terms, which is dependent on the education of the people and cultural background."	Falup-Pecurariu (2013)
Rheumatoid Arthritis	"… subscribed to disease-related factors, especially inflammation, anemia and pain. … fatigue may incorporate cognitive and emotional elements.	van Hoogmoed et al. (2010)
Sjogren's Syndrome	"… somatic and mental exhaustion that interferes with a person's ability to carry out physical and cognitive activities and can be persistent and overwhelming … differs from normal fatigue, when healthy, which is 'earned' by being physically and/or cognitively active."	Goodchild et al. (2008)
	"… complex and subjective phenomenon. Its origins are multifactorial. It is an intimate, universal and extremely frequent experience that cannot be objectively measured."	Belmont et al. (2006)
Traumatic Brain Injury	"… one of the most challenging and distressing long-term symptoms, interfering considerably with their ability to work and lead a normal life, including social activities with family and friends."	Palm et al. (2017)
Chronic Fatigue Syndrome (CFS)	"… is a multi-system complex disorder, characterized by extreme mental and physical fatigue with array of physical symptoms not relieved by rest..	Slomoko et al. (2020)

Appendix B. **Items used in this study from the Symptoms and mood questionnaires.**

Op dit moment voel ik mij **lichamelijk vermoeid** / *Right now, I feel **physically tired**.*

- Sterk mee oneens / *Strongly disagree*
- Oneens / *Disagree*
- Een beetje oneens / *Disagree a little bit*
- Neutraal / *Neutral*
- Een beetje eens / *Agree a little bit*
- Eens / *Agree*
- Sterk mee eens / *Strongly agree*

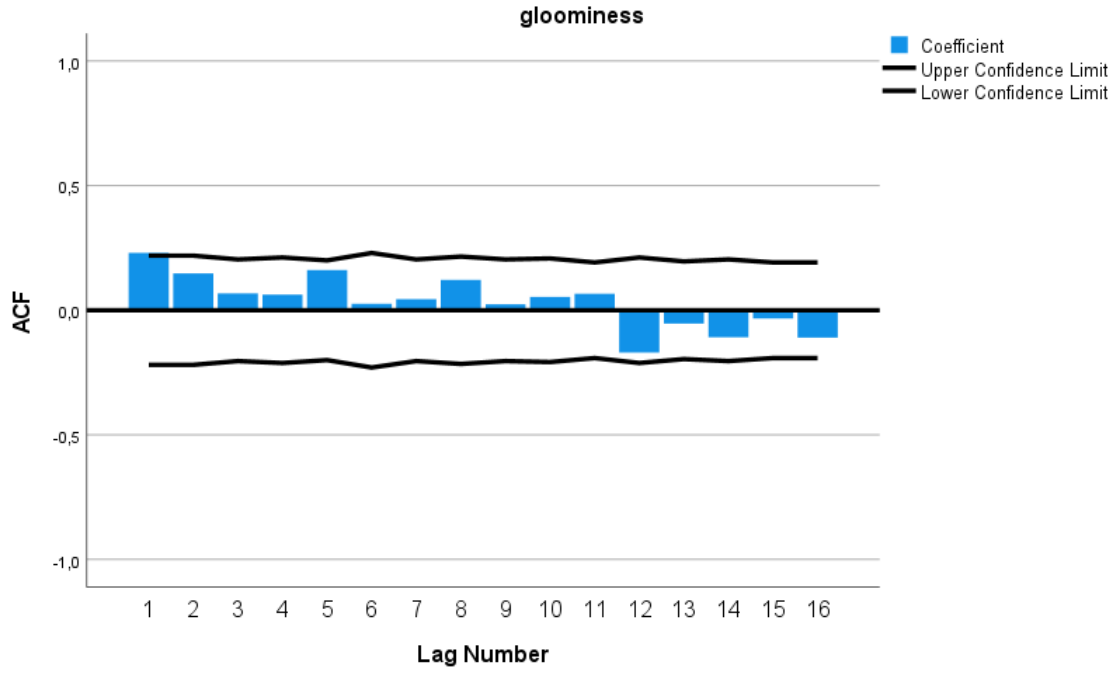
Op dit moment voel ik mij **somber** / *Right now, I feel **depressed**.*

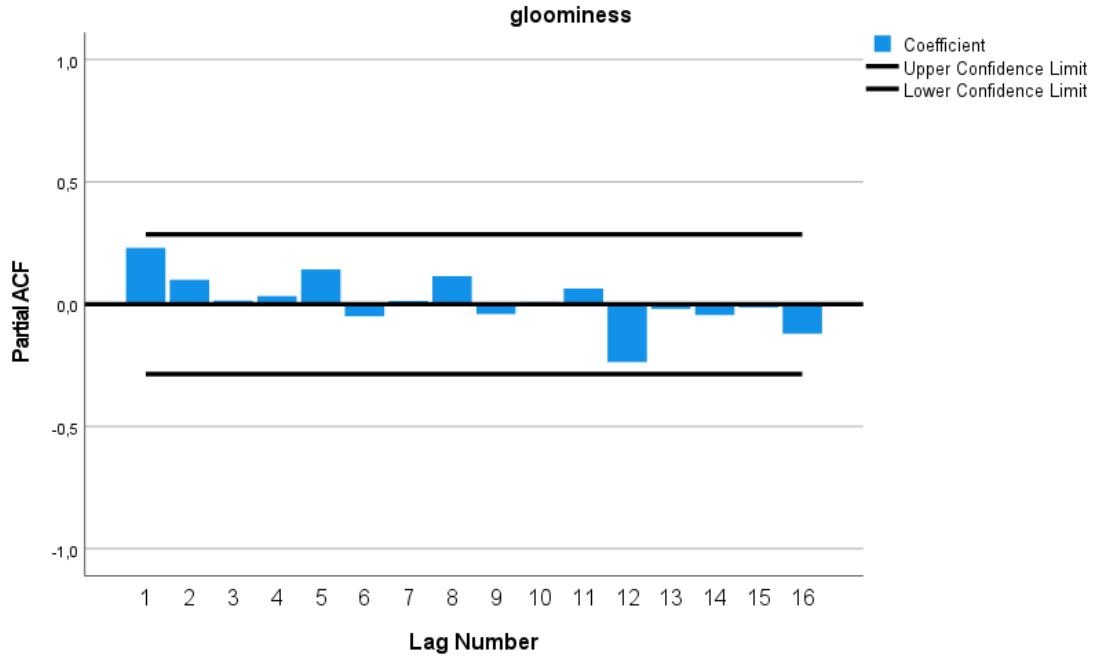
- Sterk mee oneens / *Strongly disagree*
- Oneens / *Disagree*
- Een beetje oneens / *Disagree a little bit*
- Neutraal / *Neutral*
- Een beetje eens / *Agree a little bit*
- Eens / *Agree*
- Sterk mee eens / *Strongly agree*

Appendix C**. Table of participants 3 including periodicity and autocorrelelograms for depressive mood.**

Table C Periodicity analysis

	95% CI		
43167	Lower bound	upper bound	
Timepoint total	0.002	0.014	periodicity
Timepoint day	-0.125	0.029	
day	0.016	0.084	periodicity
Week day	-0.161	-0.026	





Appendix D.

Table of Participant 5 including periodicity and autocorrelelograms for depressive mood

Table D Periodicity analysis participant 5

	95% CI		
Variables	lower bound	upper bound	
Timepoint total	-0.020	0.002	
Timepoint day	-0.186	0.126	
day	-0.122	0.011	
Week day	-0.359	-0.117	periodicity