Exploring Fatigue and Chronic Pain in Hospitalized Long-Covid Patients and the Importance of Sleeping Problems

- An Experience Sampling Method-study

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Abstract

Background. The ongoing Covid-19 pandemic had a profound effect on morbidity and mortality around the globe. Furthermore, individuals that suffered from a Covid-19 infection might develop persistent or new symptoms for several weeks or months after the infection; the so-called "long-Covid". Often occurring symptoms in long-Covid patients are fatigue, pain and sleep problems.

Objective. The current study investigated the relationships between fatigue, pain and sleep problems in hospitalized long-Covid patients over time. Moreover, it was investigated if these relationships are time specific, like a state, or time unspecific, like a trait.

Method. In this current study, the experience sampling method (ESM) was utilized, to assess the symptom experience of ten previous hospitalized long-Covid patients (M_{age}=59.7 years). The participant's symptom experience was assessed six times a day over 14 consecutive days. To examine the data, Linear Mixed Model (LMM) analyses were conducted.

Results. The results showed that fatigue (M=4.53 [1-7]), and sleep problems (M=2.19 [1-5]) were experienced by all participants to a considerable degree over time. In contrast, pain (M=2.19 [1-10]) was experienced by eight out of ten patients but only one patient had higher pain scores over time. Moreover, the pain-fatigue association (β = .33), as well as the sleep problems-fatigue association (β = .23) was found to be non-time specific, so trait-like. Furthermore, no supporting evidence could be found for a mediating effect of sleep problems on the relationship between pain and fatigue.

Conclusion. This study found, in comparison to past long-Covid studies (Davis et al., 2021; Lopez-Leon, 2021), also a high prevalence, but rather low scores of experienced pain. In contrast, similar to other studies, fatigue and sleep problems had a high prevalence and rather high scores over time within the sample. Furthermore, it was found that a long-Covid patient's momentary fatigue levels are related to a person's average pain or sleep problem levels and not to a person's pain or sleep problem levels at a specific time point. The mediation analysis showed that there is a significant relationship between pain and sleep problems, but there was no evidence found for a mediating effect of sleep problems on the relationship between pain and fatigue.

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Introduction

The ongoing Covid-19 pandemic caused substantial mortality and morbidity worldwide. Since the beginning of the pandemic, there were globally over 434 million cases and nearly 6 million deaths reported (Worldometer, 2022). Regarding the hospitalisation of Covid-19 cases, no institute or paper summed up the global total hospitalization rate. However, most countries do report an average number of hospital admissions per week. For instance, in the first wave of the Covid-19 pandemic in the Netherlands, there were around 3.000 hospital beds (6,02%) and 1.400 (3,12%) ICU beds occupied by Covid-19 patients (*Current situation in the Netherlands,* 2022). Moreover, even after discharge from the hospital, a subset of the individuals that got infected by Covid-19 developed persistent or new symptoms for several weeks or months; the so-called "long-Covid" syndrome (Alwan, 2021). In more recent articles, this syndrome is not addressed as the long-Covid syndrome anymore but as the "post-Covid" syndrome (Ceban et al., 2022). However, this paper was written before the term has changed wherefore in this paper it will be addressed as long-Covid. To add new knowledge to the novel field of long-Covid, this study aims to further investigate its most prevalent symptoms, fatigue, and pain, in hospitalized long-Covid patients using an ESM study design. Furthermore, the role of sleep problems within this relationship will be investigated.

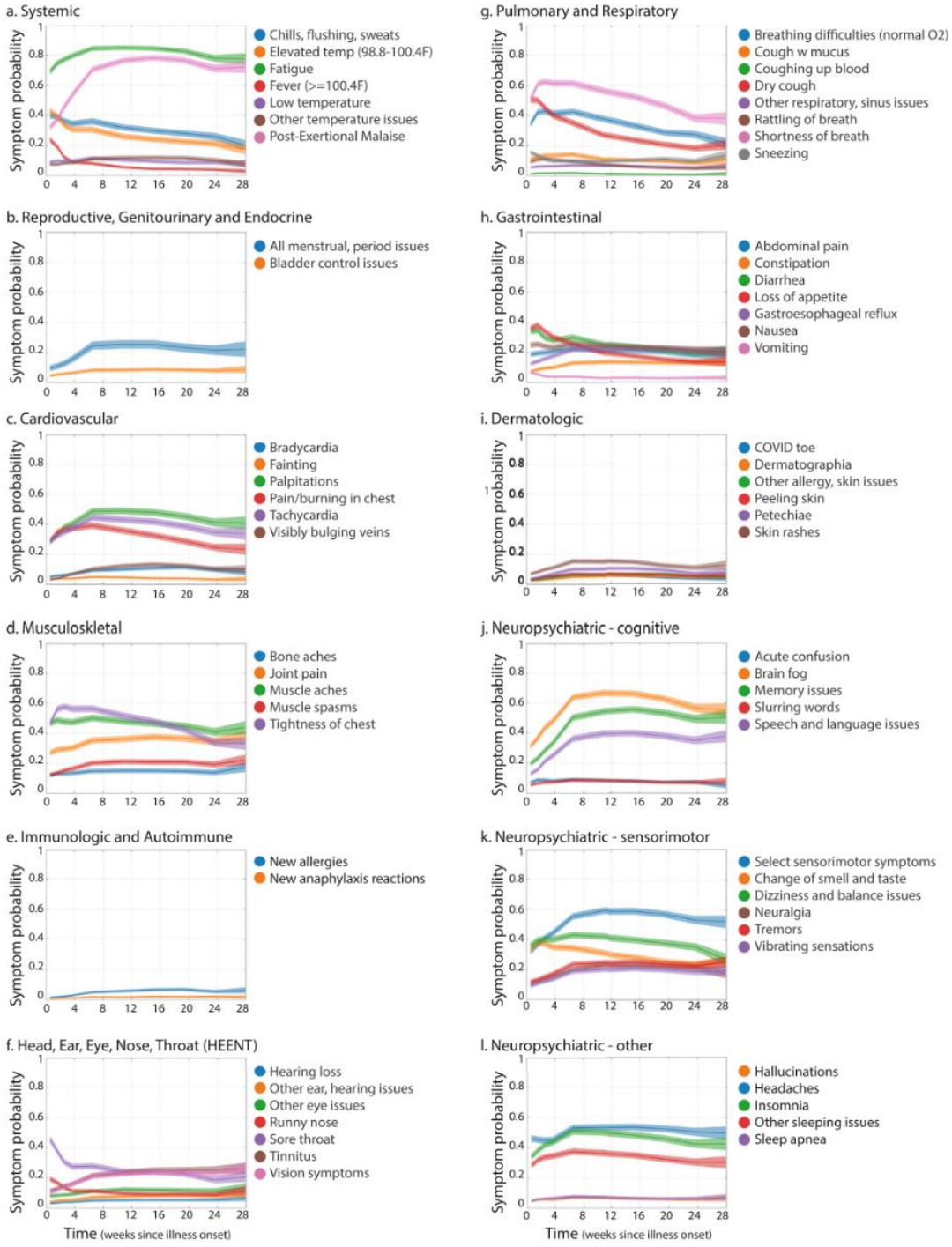
Present research about long-Covid

The literature about concrete numbers of long-Covid cases is, due to its novelty, still limited. However, a frequently cited report from Italy stated that 60 days after the onset, 87% of individuals that recovered from Covid-19 and were discharged from the hospital showed persistence of at least one Covid-related symptom (Raveendran, Jayadevan & Sashidharan, 2021). Moreover, among these recovered individuals, "32% had one or two symptoms, and 55% had three or more" (Mahase, 2020, p.2). Regarding the symptomology of long-Covid, many papers all report different sets of symptoms, resulting in an overall extensive and widely varying group of symptoms. This diversity and the extensiveness of possible symptoms from long-Covid patients is represented by a figure from Davis et al. (2021) (Figure 1). In the long-Covid literature, there are differences in the number of symptoms that were found, but there are similarities in the most prevalent symptoms. For instance, the symptoms that were stated as one of the most prevalent in the articles by Davis et al. (2021), Lopez-Leon et al. (2021), Mahase (2020) and Mandal (2021) were fatigue (53.1-69%), breathlessness/ dyspnoea (24-

53%), and chronic pain in form of headache (44%), joint (19-27%) and chest pain (16-21%). Moreover, the most prevalent psychological symptoms were anxiety (13%) and depression (12-14%) (Lopez-Leon et al., 2021; Mahase, 2020; Mandal, 2021). These overlapping results can also be seen in the figure from Davis et al. (2021) (Figure 1) and Lopez-Leon et al. (2021) (Figure 2). Therefore, based on the literature this study will focus on two of the most prevalent long-Covid symptoms fatigue and chronic pain, including headache, joint and chest pain. Even though dyspnoea was also stated as a symptom with a high prevalence in the long-Covid literature, it was not included in this study. Due to time limitations, only a selection of symptoms could be included and since dyspnoea had a large variance in the percentages (24-53%) it was excluded.

Figure 1.

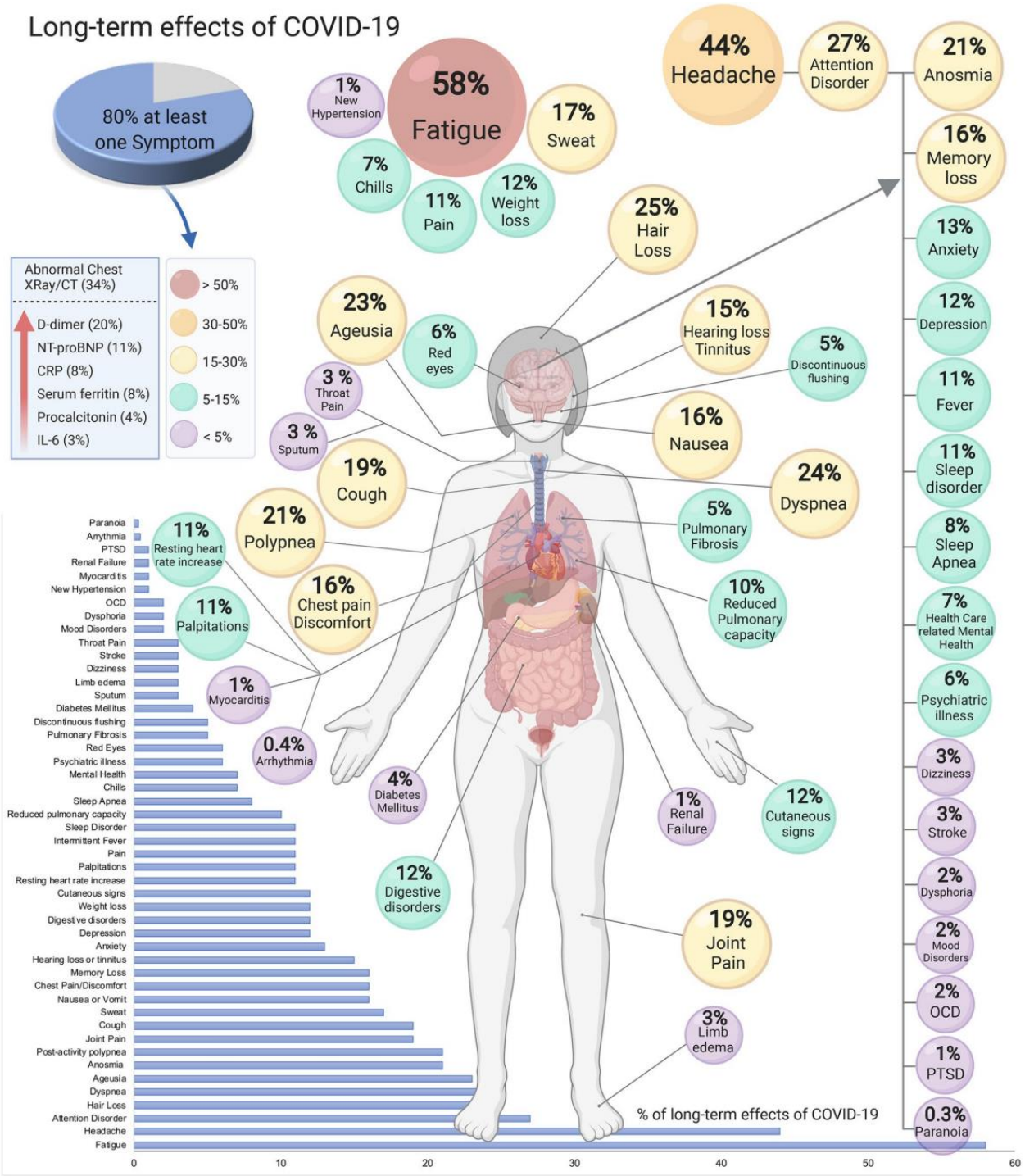
The figure represents the estimated probability of experiencing each symptom at each time point in long-Covid patients.



Note. From *Characterizing long-Covid in an international cohort: 7 months of symptoms and their impact*, by H.E. Davis et al., 2021, p. 7.

Figure 2.

The figure represents the long-term effects of the coronavirus disease based on a meta-analysis of long-Covid studies.



Note. From *More than 50 long-term effects of COVID-19: a systematic review and meta-analysis,* by S. Lopez-Leon et al., 2021, p. 9.

Fatigue in long-Covid

Since there is only limited literature on fatigue and pain in long-Covid patients, literature about other chronic diseases with these symptoms was used to gather information about these symptoms. For instance, fatigue is a common symptom of many chronic diseases like Parkinson's disease, multiple sclerosis, or cancer (Flachenecker et al., 2006; Lou et al., 2001; Vollbracht & Kraft, 2021). Moreover, fatigue is also a principal characteristic of depression and generalised anxiety disorder (Friedman & Chou, 2004). Fatigue is a multi-layered symptom ranging from mental depression to muscular weakness. Therefore, fatigue can be divided into two distinct own symptoms, namely "mental fatigue" and "physical fatigue" (Lou et al., 2001). However, studies have shown that long-Covid patients often suffer from both mental and physical fatigue (Van Herck et al., 2021). Regardless, in the majority of long-Covid research, there is no distinction made between mental and physical fatigue (see Davis et al., 2021; Lopez-Leon et al., 2021). Therefore, to allow for a better comparison of the results, this paper also not distinguished between mental and physical fatigue.

In most cases of long-Covid, fatigue is not a persistent symptom, and also in patients that suffered from post-Covid fatigue, the symptom will most often gradually resolve (Shepherd, 2021). However, in cases where symptoms such as disabling fatigue, unrefreshing sleep, and cognitive dysfunction remain for more than 6 months, it can develop into chronic fatigue syndrome (also called Myalgic Encephalomyelitis, therefore the abbreviation ME/CFS) (Afari & Buchwald, 2003; Lim & Son, 2020). ME/CFS may also be relevant for long-Covid patients since early studies into long-Covid symptomatology showed similarities between ME/CFS and fatigue in long-Covid patients (Wong, 2021). Furthermore, an article by Shepherd (2021) suggests that it would be more appropriate for people with long-Covid to diagnose their fatigue as post-Covid ME/CFS instead of long-Covid, at least for those cases suffering from persistent symptoms of ME/CFS for more than three or four months and in which the condition is not related to heart or lung damage. The results of the study by Wong (2021) and Shepherd (2021) indicate an association between fatigue in long-Covid patients and the symptomology of ME/CFS patients. Furthermore, the paper by Lim and Son (2020) indicates the need for immediate handling of fatigue in long-Covid patients, to prevent the development of ME/CFS.

Because of the impact fatigue has on patients, there is a great interest in finding possible causes of fatigue. However, despite the extensive research on fatigue, the causes are still poorly understood and not directly treatable (Friedman & Chou, 2004; Stanton, Barnes &

Silber, 2006). This study aims at adding knowledge to the understanding of fatigue and at investigating possible determinants of fatigue.

Chronic pain in long-Covid patients and its association with fatigue

Another common symptom described by long-Covid patients next to fatigue are different types of chronic pain. Regarding the area of pain, Lopez-Leon et al. (2021) found headache to be the most prevalent type of pain. In contrast, a study by Aiyegbusi et al. (2021) stated that joint, muscle and chest pain are the most occurring pain symptoms.

Syndromes defined by fatigue and chronic pain have been a prominent topic in medical literature for centuries. The origin of chronic pain was mostly attributed to musculoskeletal features, so bones, muscles, tendons, ligaments and soft tissues; however, recent findings show that there is a great amount of non-musculoskeletal pain symptoms that overlap with associated conditions such as MF/CFS (Claliw, 1995). Moreover, Mastaglia (2012) assumes that the reduction of chronic pain may have an impact on the patient's fatigue. Furthermore, Mastaglia (2012) proposes that there is a close association between pain and fatigue, that still needs further investigation. However, to our knowledge, studies investigating the specific association between pain and fatigue in long-Covid patients are not yet published.

The role of sleep

Previous studies have not only found an association between chronic pain and fatigue but also between chronic pain and sleep problems. The relationship between sleep and pain is a prominent topic in the literature; however, the direction is poorly understood (Moldofsky, 2001). For instance, a study by Sivertsen et al. (2015) showed that with an increase in sleep problems there is a decrease in an individual's pain tolerance. In contrast, there is also evidence that chronic pain is related to sleep disturbance, indicating the bidirectional nature of this association (Roehrs & Roth, 2005). The relation between sleep problems and pain in long-Covid patients has not been studied yet, literature focused solely on the association of sleep and pain as part of living in the Covid-19 pandemic in healthy individuals, but not in Covid or long-Covid patients.

The role of sleep problems might also be important for long-Covid patients suffering from fatigue. There is no research yet on the determinants of fatigue in long-Covid patients, however, a study with a group of multiple sclerosis patients that suffered from fatigue

indicated an association between sleep disturbance and daytime fatigue (Stanton, Barnes & Silber, 2006). In contrast to fatigue, sleep disorders are often responsive to therapy (Friedman & Chou, 2004) such as medication, sleep hygiene advice, or cognitive behavioural therapy (Côté et al., 2012), which increases the interest in researching an association between sleep and fatigue in long-Covid patients.

To investigate the recent field of long-Covid, the study described in this paper has further assessed the associations between fatigue, chronic pain, and sleep problems in long-Covid patients. To not only achieve insight into the differences between the patients, but to also view individual differences within the patients, the experience sampling method was used. In this research method, the participants fill out daily measures to obtain extensive individual data over time. Through this procedure, a score measured at one point of a participant can be compared with the same participant's individual mean score calculated from all measures, but also with the mean score of the whole sample. Therethrough, the between- and within-person associations, and their differences, can be assessed. Based on the prevalence and high burden fatigue and chronic pain have on their patients and the promising research about sleep problems as a possible missing link, the research questions of this paper will be:

Research question 1: *How are fatigue, pain and sleep problems experienced by long-Covid patients over time?*

Research question 2: *How are pain and sleep problems related to fatigue over time between and within long-Covid patients?*

Moreover, due to the supposed association between chronic pain and sleep problems that were found in the literature, this research will investigate the hypothesis that chronic pain is not directly related to subsequent fatigue, but rather chronic pain related to subsequent sleep problems, which in turn is related to subsequent fatigue.

Hypothesis: *The relationship between chronic pain and fatigue is partially mediated by sleep problems.*

Methods

Participants and Procedure

The current study uses the data from an ongoing cohort study from the hospitals Medisch Spectrum Twente (MST; Enschede) and Ziekenhuis Groep Twente (ZGT; Almelo and Hengelo). The original cohort study investigates hospitalized patients with a SARS-CoV-2 infection at 0,3,6,9 and 12 months after hospital discharge. 42 previously hospitalized patients were selected to self-report their health status in comparison to one year ago, prior to the COVID hospitalization. Participants that were categorized as non-recovered ('health much worse as a year ago'; n=32) were selected for an interview. In these interviews, the recovery status of the participants was reassessed based on the participants' responses in the interview.

Inclusion criteria for the interview study were a minimum age of 18 years, proficiency in Dutch language and a discharge from the hospital after an acute Covid-19 infection (PCR-confirmed). Participants that fulfilled the inclusion criteria were invited to an interview by mail. Furthermore, the participants were asked to fill out a detailed patient information sheet and an informed consent. A final sample of 8 recovered and 16 non-recovered patients were interviewed. All patients were discharged from the hospital between September 2020 and February 2021 and had been interviewed between 7 and 12 months after hospital discharge. Moreover, the study was approved by both the Medisch Spectrum Twente Institutional Review Board (request K20-30) and the ethical committee of the Faculty of Behavioural, Management and Social Sciences of the University of Twente (request 210799). After the interview process, 11 of the 16 non-recovered participants were selected for the ESM study but one had to be excluded based on the required compliance rate of 30% or more of the ESM measures (Delespaul, 1995). Therefore, this current ESM study had a sample of N=10. The additional inclusion criteria for the ESM study were a severe impact by fluctuating symptoms such as pain, fatigue, cognitive dysfunction and/or dyspnoea that were at least primarily attributed to long-Covid by the patient.

Within the sample, gender was equally distributed with five women and five men. The mean age of the sample was 59.7 years (SD=7.65), ranging from 48 years to 76 years. Furthermore, all but two participants had one or more comorbidities.

Materials

Ethica app

For the distribution of the surveys, the smartphone application Ethica was used (Ethica data, 2020). The participants received seven daily surveys on the Ethica app. Firstly, in the morning a retrospective sleep survey, asking for the duration and the quality of the participants' sleep. Secondly, six surveys were distributed over the day asking about the momentary behaviour and feelings of the participants. There were in total 16 variables that were measured in the ESM study, but for this paper only the variables fatigue, pain and sleep problems were relevant.

Fatigue

Fatigue was measured on the mental and the physical level. Physical fatigue was measured using a 7-point Likert scale (1 strongly disagree- 7 strongly agree), based on an item from the Patient Health Questionnaire (PHQ)-9 (Kroenke et al., 2001). The item to assess physical fatigue was: "At the moment I feel more physically tired than usual at this time". The mental fatigue measure was based on an item from the Wood Mental Fatigue Inventory (Bentall et al., 1993), and used a 7-point Likert scale (1 strongly disagree- 7 strongly agree) as well. The item to assess mental fatigue was:" Right now I feel more drowsy and tired in my head than usual at this time". The items are consistent with ESM studies on fatigue in other chronic conditions (Brys et al., 2020; Lenaert, Neijmeijer, et al., 2020), which provides a good picture of daily and weekly fluctuations in fatigue (Lenaert, van Kampen, et al., 2020). Physical fatigue and mental fatigue showed good reliability (α=.86) and a significantly strong correlation (r=.76). Therefore, the item of mental and physical fatigue was combined into a general fatigue variable.

Pain

Pain was firstly assessed on a general level by answering yes or no. If the participants answered yes, the specific pain was assessed: "I'm suffering from [Headache; Joint pain; Chest pain] at the moment". The participants did not have to choose one option, they could choose also two or more types of pain. The intensity of the general and specific pain was assessed on a scale from 0 (no pain) to 10 (most excruciating pain). If the participants answered no on the general level, then they received a 0 for the specific pain items. To see if the specific pain items can be combined, a reliability analysis and a partial correlation analysis by controlling for all timepoints were conducted. The specific pain items showed good

reliability (Cronbach's α=.82) and significant moderate to strong correlations ($r_{head\&chest}$=.83, $r_{head\&joint}$=.53, $r_{chest\&joint}$=.64). Therefore, the items headache, joint pain and chest pain were combined into a general pain variable.

Sleep

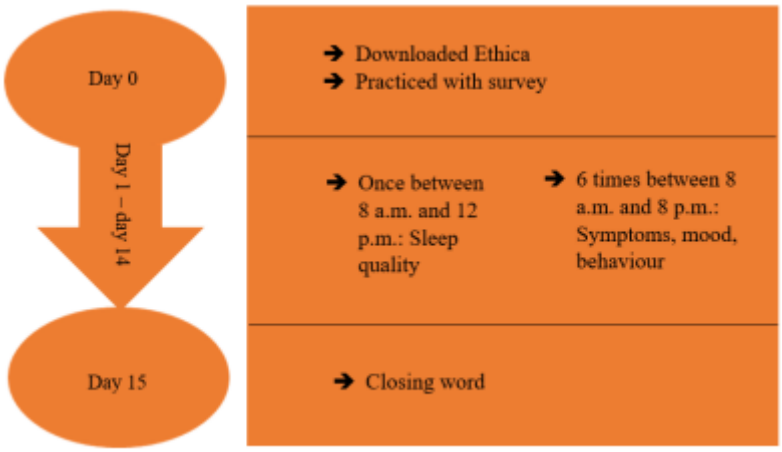
Sleep was measured on two levels, in terms of sleep quality and sleep duration. The sleep quality was measured with one item, and similar to the more extensive questions of Brys et al. (2020) and Jean et al. (2020). The sleep quality item was: "To what extent did you suffer from problems sleeping last night?". It was assessed with a Likert scale from 1 (none) to 7 (a lot). The sleep duration was assessed by asking for the number of hours slept. The options were less than 4 hours, 4-6 hours, 6-8 hours, 8-10 hours, and more than 10 hours. However, this item was mainly included to help the participants to better estimate the quality of their sleep. Therefore, in this study, only the sleep quality measure was used to create the sleep problem variable which was further used.

Design

The design of this ESM study is based on the guidelines of Conner and Lehman (2012). As suggested by Hektner et al. (2007) the study lasted for 14 consecutive days. Figure 2 represents a visual overview of the duration of the study. The ESM study used the so-called signal-contingent sampling strategy. This strategy entails that the participants receive, within equal two-hour time intervals, notifications on random intervals throughout the day that remind the participants to fill out the survey. The participants received a total of seven surveys together with a notification per day. After 15 minutes the notification disappeared to reduce the burden on the participants, so they were less likely to be annoyed by the notifications.

Figure 3

Flowchart of the study design



Note. From *Physical and mental fatigue and their risk factors in people with long-Covid after hospital discharge,* by M. Wensink, 2022, p.13.

Data analysis

To begin the data analysis, the data was firstly exported from Ethica into the statistical program IBM SPSS Statistics 25. In order to prepare the data for further analyses, all participants were excluded that had a response rate of less than 30%. Afterwards, the variables fatigue and pain were computed. Therefore, a reliability and correlation analysis were conducted to investigate if mental and physical fatigue can be combined into a general fatigue variable and if headache, joint, and chest pain can be combined into a general pain variable. Afterwards, based on the good reliability and significant correlations, the variables were computed by calculating a mean score. Moreover, since this study is interested in pain as a predictor of sleep problems, a second pain variable was created which represents the pain from one day earlier. Therefore, the variable was lagged six times since there were six measures per day, so it became the pain yesterday variable. Furthermore, all scores from the now four relevant variables, fatigue, pain, pain yesterday and sleep were transformed into z-scores to allow for comparison. This step was conducted since the variables were measured on different scales, for instance, pain was measured on a scale of one to ten while fatigue and sleeping problems were measured with a 7-point Likert scale.

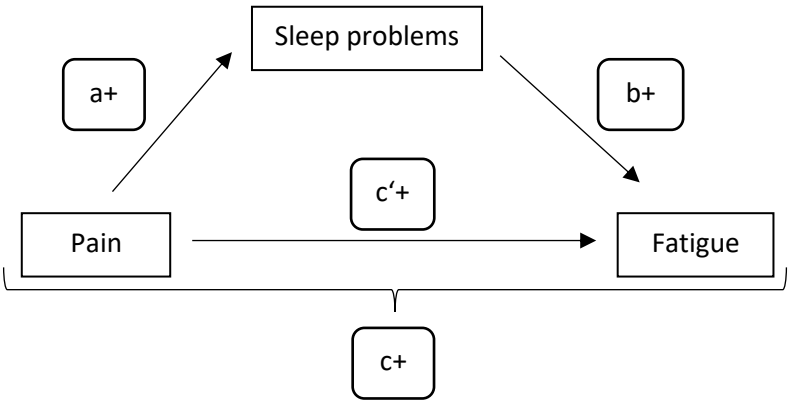
After the data preparation, descriptive statistics were assessed as raw and z-scores, to be able to interpret the meaning of the fatigue, pain, and sleep problems levels. Furthermore,

the mean scores were visualized over the time points to get an insight into the variable scores. Next, to answer the research questions first, the mean scores of pain and fatigue were represented for each individual over the day, summed over the fourteen days of the study. Moreover, the mean scores of fatigue, pain and sleep problems were also visualized over the 14 days of the study of each participant. Second, two linear mixed model analyses (LMM) were conducted to investigate the association between chronic pain, sleep problems and fatigue over time. Afterwards, the between- and within-person associations of chronic pain with fatigue were assessed. In the first analysis, the raw score of fatigue was used as the dependent variable and the person mean scores and person mean centred scores of chronic pain were the covariates. In the second analysis, the fatigue raw scores were still used as the dependent variable, but the person mean scores and person mean centred scores of sleep problems were then used as covariates. Afterwards, the association between fatigue and the person mean scores will represent the between-person association, and the association between fatigue and the person mean centred score will represent the within-person association. In sum, these analyses investigated the differences in the association of chronic pain and sleep problems with fatigue between the participants and individually within the participants.

Furthermore, to test the hypothesis "*The relationship between chronic pain and fatigue is partially mediated by sleep problems.*" three LMM analyses were conducted. As described by Baron and Kenny (1986) three LMM analyses were conducted to test for a mediation. First, to find out the total effect *c* the relationship between the independent variable pain yesterday and the dependent variable fatigue was assessed. Second, to calculate the indirect effect *a* of the relation from the independent variable pain yesterday with the mediator variable sleep problems as the dependent variable was conducted. Thirdly, to assess the direct effect *c'* and the indirect effect *b* an analysis with the independent variables pain yesterday and sleep problems as well as with the dependent variable fatigue was operated (see figure 4).

Figure 4

A theoretical model of the relationship between fatigue, pain and sleep problems



Results

Firstly, the mean scores of the total sample over the total assessment period from the raw and z-scores of the variables fatigue, pain, and sleep problems are represented in table 1. In this table, it can be seen that the participants experienced generally low levels of pain. In contrast, the mean fatigue score was rather high, while sleep problems seem to be balanced.

Table 1

Descriptive statistics of the raw and z-scores of the variables fatigue, pain, and sleep problems.

	N	Minimum	Maximum	Mean	Std. Deviation
Fatigue	502	1	7	4.53	1.56
Pain	499	1	10	2.19	2.50
Sleep problems	724	1	5	2.17	0.98
Z Fatigue	502	-2.26	1.59	0.00	1.00
Z Pain	499	-0.88	2.58	0.00	1.00
Z Sleep problems	724	-1.20	2.90	0.00	1.00

Secondly, the mean scores were investigated over time. As can be seen in figure 5, which represents the participants' mean fatigue, pain and sleep problem scores over all days during the assessment period, there were large fluctuations within the variables on a group level. Furthermore, it can be seen that the largest fluctuations were for the pain and fatigue scores, whereby the sleep problem scores show smaller fluctuations.

Moreover, also a clear association can be seen between the three variables. This association becomes even more apparent in figure 6, where the z-scores are represented over time. Furthermore, in these two figures, it can be seen that around measures 56 and 61 there was a large drop in fatigue, pain and sleep problem scores.

Figure 5

Mean scores of fatigue (blue), pain (red) and sleep problems (green) over all 84 measurement points (7 measures per day for 14 days).

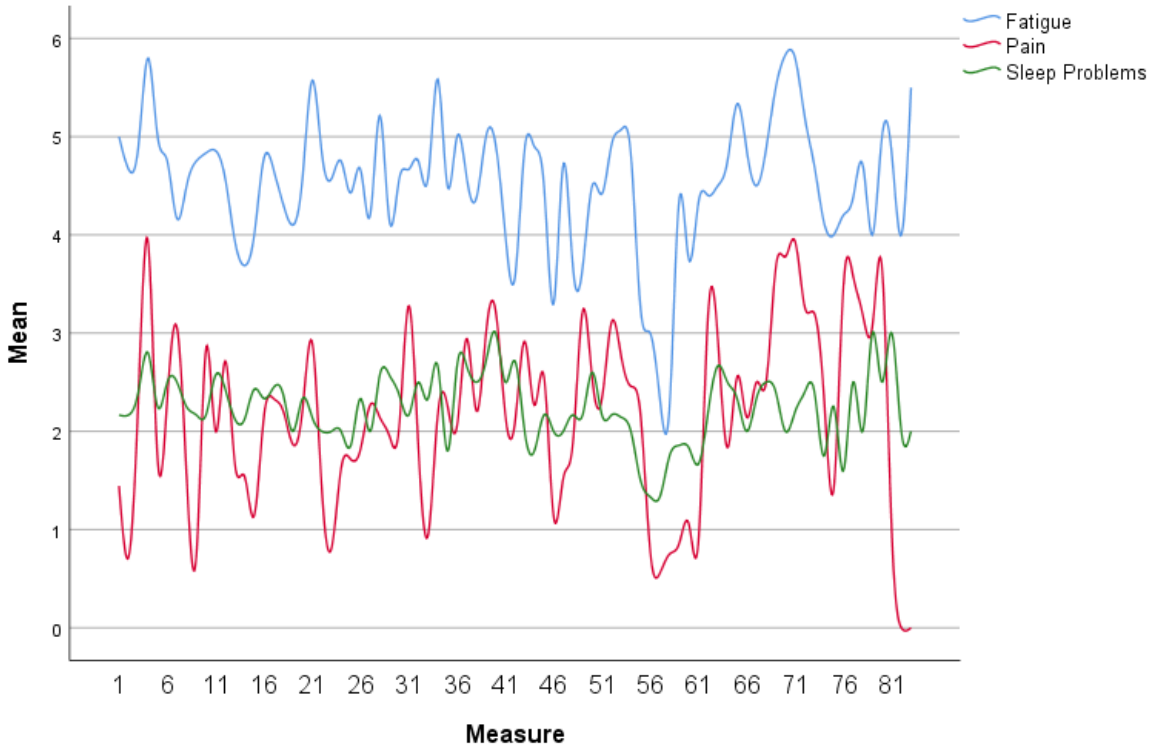
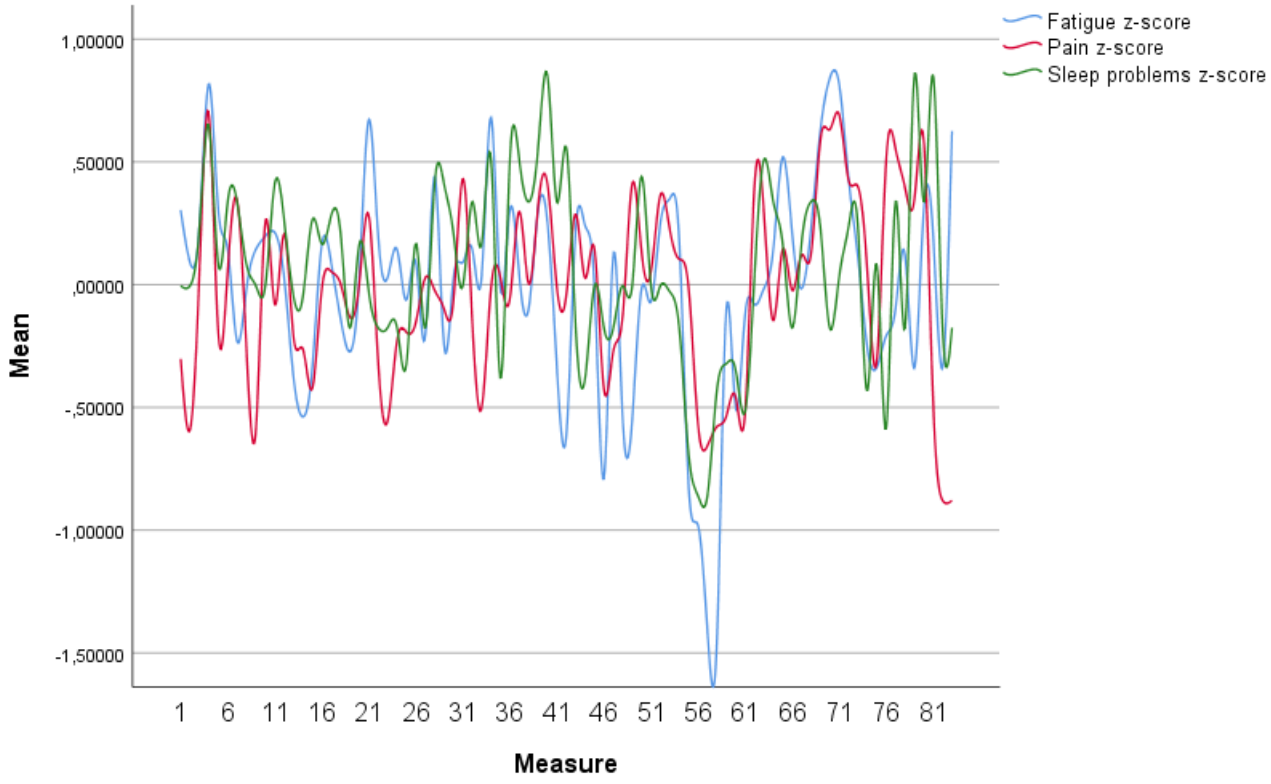


Figure 6

Mean z-scores of fatigue (blue), pain (red)and sleep problems (green) over all 84 timepoints (7 measures per day for 14 days).



Moreover, figure 7 and figure 8 represent the mean fatigue and pain scores over the day summed over the fourteen days of the study for the different participants. In these figures it can be seen, that for most participants, there are fluctuations over the day, for fatigue more than for pain, but in general these are rather small. Furthermore, as can be seen in figure 7, all participants experienced fatigue and most of them had rather high scores. In contrast, in figure 8 it is apparent that most participants experienced rather little pain and two of them experienced no pain at all. However, there was one participant that experienced significantly more pain, than the rest of the sample.

Figure 7

Mean fatigue scores over the day, summed over the fourteen days of the study for the different participants.

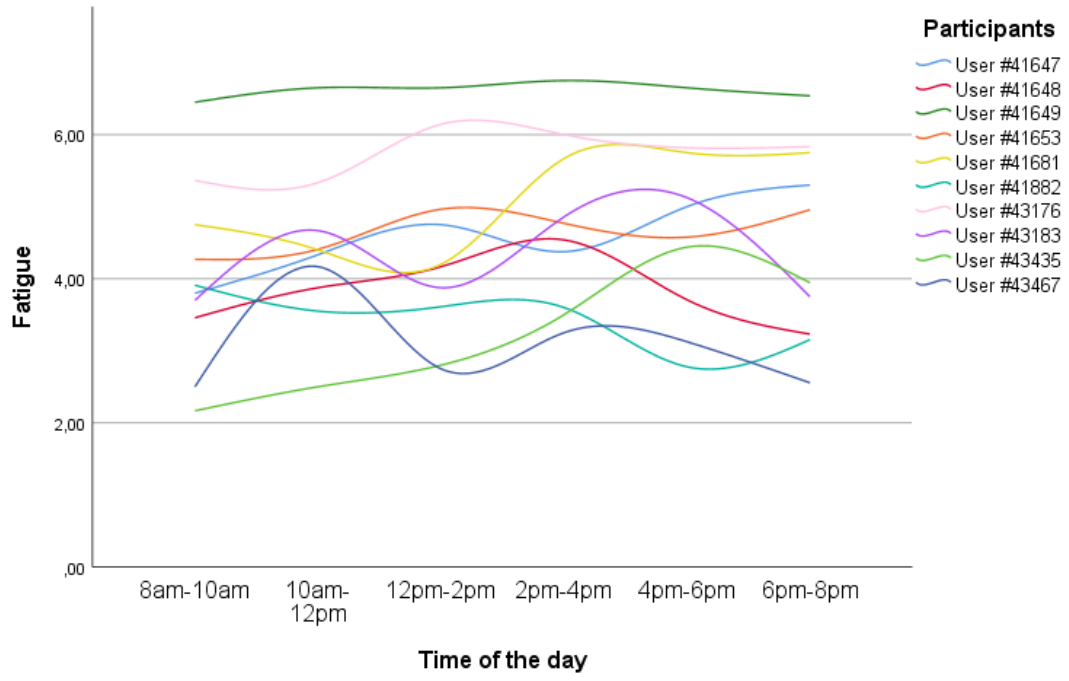
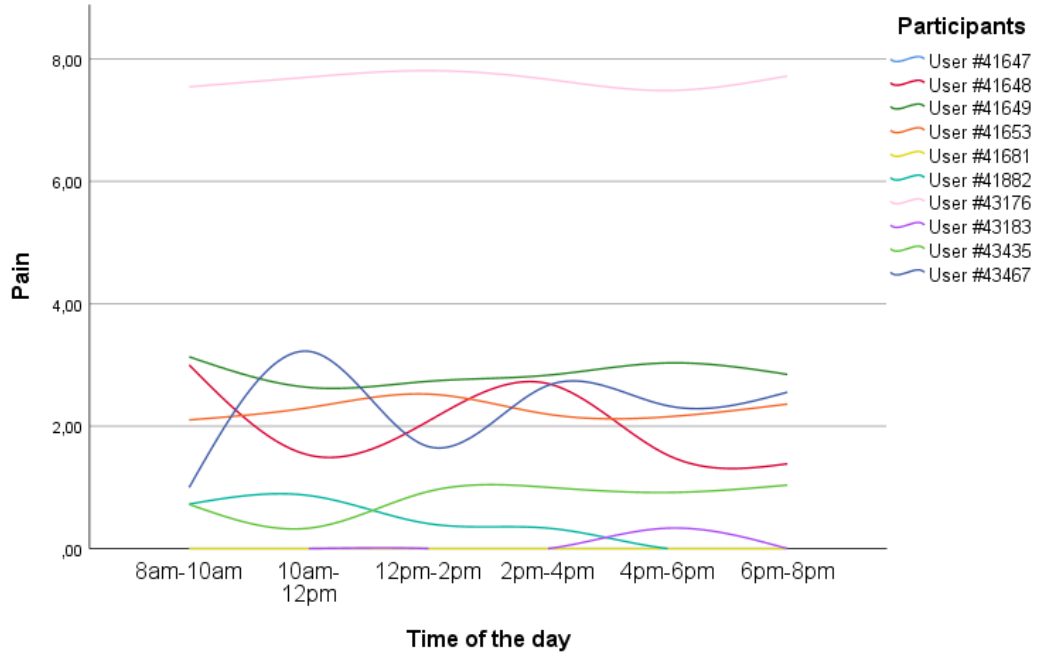


Figure 8

Mean pain scores over the day, summed over the fourteen days of the study of different participants



Furthermore, figures 9 to 11 display the separate mean pain, fatigue, and sleep problem scores over the fourteen days of the study of the different participants. In contrast to Figures 7 and 8, there are much larger fluctuations for all three variables. Moreover, both participants that had the highest scores in Figures 7 and 8, show rather small fluctuations in Figures 9 and 10 in comparison to the other participants.

Figure 9

Mean fatigue scores over the fourteen days of the study of the different participants

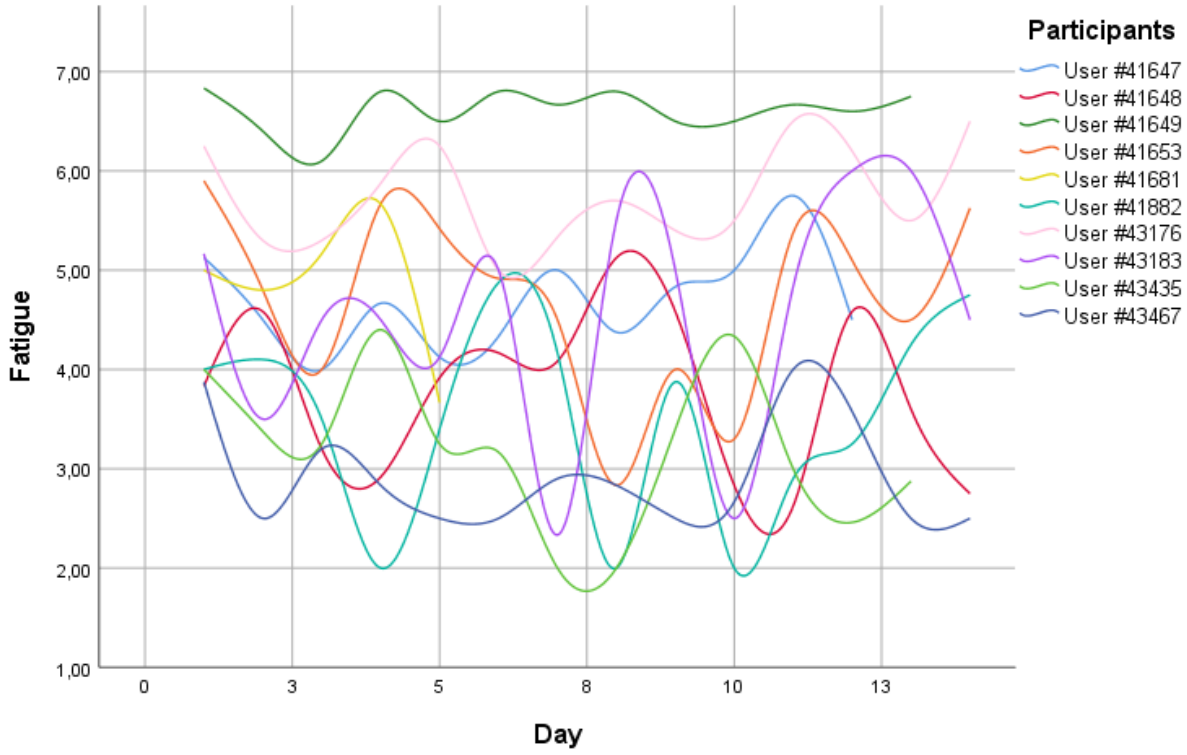


Figure 10

Mean pain scores over the fourteen days of the study of the different participants

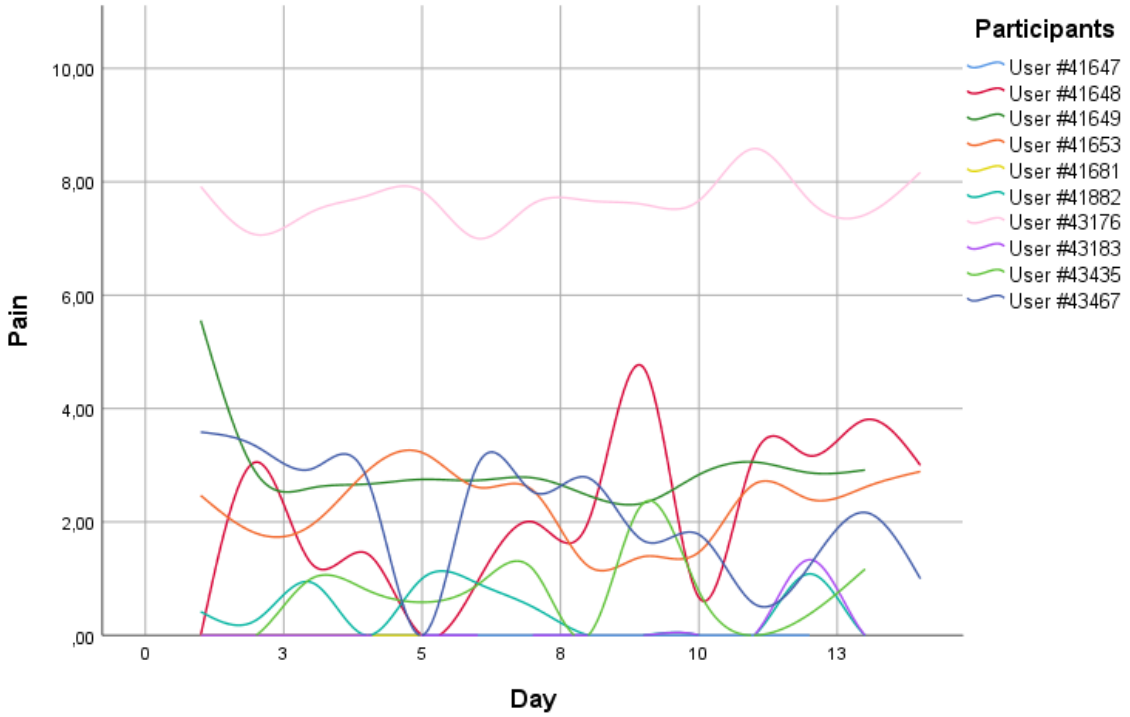
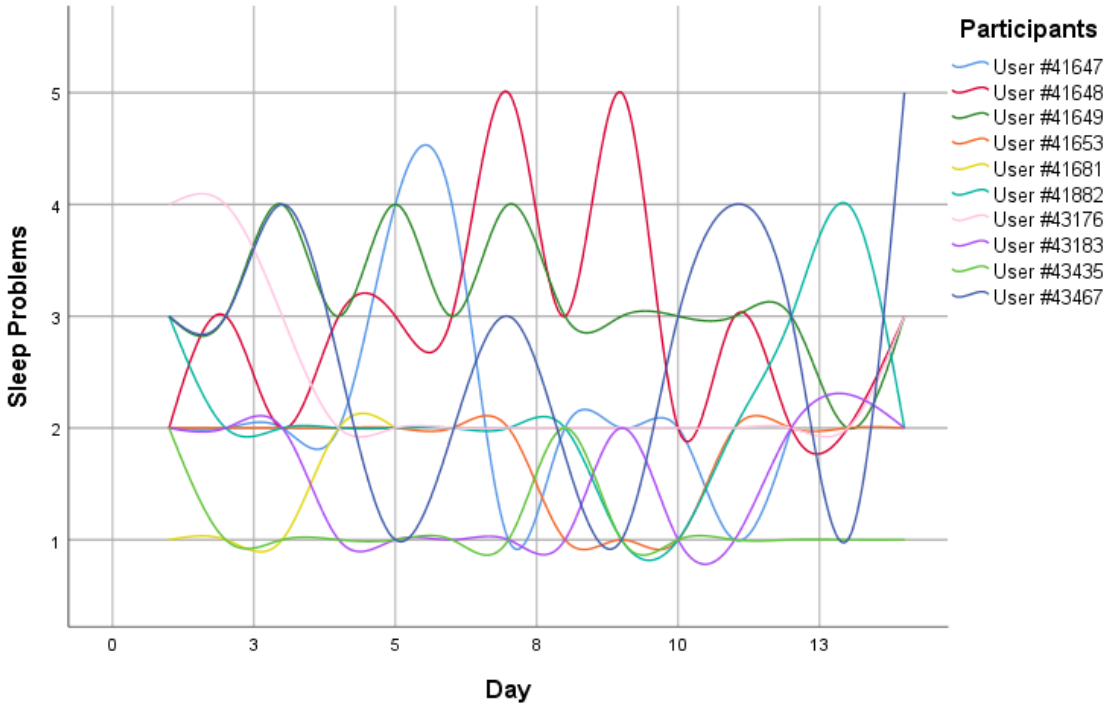


Figure 11

Mean sleep problems scores over the fourteen days of the study from the different participants



Thirdly, the associations between pain and fatigue over time were investigated. As can be seen in table 2, the between-person association, as well as the within-person association for pain and fatigue were significant. However, the standardized between-person association (β = 0.33) between pain and fatigue is clearly stronger than the within-person association (β = 0.19). These results indicate that the association between pain and fatigue at a certain time point appears to be mainly a between-person association and not so much a within-person association.

Therefore, participants with higher pain scores on average than others, have higher fatigue scores at the different time points. Moreover, at time points where patients have a higher or lower pain score than their own average, this is also weakly associated with a higher or lower fatigue score at that time point.

Table 2

Between-person (PM) and within-person (PMC) associations of pain as covariate and fatigue as the dependent variable.

DV: Fatigue	Estimate (95% CI)	t (df)	p-value
Pain PM	.33 (.16, .50)	3.94 (53.549)	.000
Pain PMC	.19 (.14, .24)	6.91 (404.984)	.000

Note. These results were composed from a data set of a longitudinal study over 14 days in 10 participants, calculated with an LMM analysis. For the calculations, the standardised scores of the variables fatigue, pain and sleep problems were used.

Fourth, the associations between sleep problems and fatigue over time were investigated (see table 3). In this analysis, only the between-person association (β = .23) between sleep problems and fatigue was significant, but not the within-person association. These results indicate that the association between sleep problems and fatigue at a certain time point are only between-person associations.

Accordingly, participants that scored higher in sleep problems on average than others, have higher fatigue scores at the different time points. Furthermore, at time points where patients have a higher or lower sleep problem score than their own average, this is not associated with a higher or lower fatigue score at that time point.

Table 3

Between-person (PM) and within-person (PMC) associations of sleep problems as covariate and fatigue as the dependent variable.

DV: Fatigue	Estimate (95% CI)	t (df)	p-value
Sleep problems PM	.23 (.05, .41)	0.77 (53.525)	.013
Sleep problems PMC	.04 (-.06, .15)	0.77 (398.986)	.440

Note. These results were composed from a data set of a longitudinal study over 14 days in 10 participants, calculated with an LMM analysis. For the calculations, the standardised scores of the variables fatigue, pain and sleep problems were used.

Fifth, for the mediation, three LMM analyses were conducted as described by Baron and Kenny (1986). The first LMM analysis was done to assess the total effect with the dependent variable fatigue and the independent variable pain yesterday. As seen in table 4, the effect was not significant. The second LMM analysis was conducted to assess the indirect effect of the independent variable pain yesterday on the mediator sleep problems. Different to the other analysis, the effect of pain yesterday on sleep problems was significant (Table 5). In the third LMM analysis, fatigue was the dependent variable and pain yesterday and sleep problems were the independent variables. As seen in table 6, the effect of pain yesterday on fatigue was significant, in a model together with the effect of sleep problems. However, the effect of sleep problems on fatigue was not significant.

In conclusion, these results represent that there is no mediating effect of sleep problems on the association between pain yesterday and fatigue and therefore the hypothesis needs to be rejected.

Table 4

LMM analysis with pain yesterday as the independent variable and fatigue as the dependent variable, to calculate the total effect c.

DV: Fatigue	Estimate (95% CI)	t (df)	Sig.
Pain yesterday	.11 (-.01, .23)	1.87 (292.196)	.062

Table 5

LMM analysis with pain yesterday as the independent variable and sleep problems as the dependent variable, to calculate the indirect effect a.

DV: Sleep problems	Estimate (95% CI)	t (df)	Sig.
Pain yesterday	-.06 (-.12, -.00)	-2.10 (464.254)	.036

Table 6

LMM analysis with pain yesterday and sleep problems as the independent variable and fatigue as the dependent variable, to calculate the indirect effect b and the direct effect c'.

DV: Fatigue	Estimate (95% CI)	t (df)	Sig.
Pain yesterday	.13 (.02, .25)	2.25 (262.754)	.025
Sleep problems	.14 (-.01, .29)	1.96 (120.606)	.053

Discussion

In this longitudinal ESM study, the relations between the variables fatigue, pain and sleep problems were investigated, among hospitalized long-Covid patients. The aim of this study was to add knowledge to the novel field of long-Covid and in particular to the understanding of these often occurring symptoms. Therefore, the purpose was to investigate if the associations between pain and sleep problems with fatigue in long-Covid patients are time specific (state-like) or time unspecific(trait-like). Moreover, the mediating effect of sleep problems on the relationship of pain and fatigue was tested.

Main findings

Symptom prevalence and experience over time

First, to answer the first research question "How are fatigue, pain and sleep problems experienced by long-Covid patients over time?", the impact of the symptoms over time will be described. Additionally, the prevalence of the symptoms within this study will be compared with previous studies.

Similar to the findings of Davis et al. (2021) and Lopez-Leon et al. (2021), fatigue was one of the most prevalent symptoms within the sample. However, there were large fluctuations among the participant over the 14 days of the study. In contrast, there were only small fluctuations for the experienced fatigue over the day (8 am-8 pm). The finding that there were no large fluctuations in the fatigue scores over the day, differs from the results in the study by Powell et al. (2017), in which they observed fatigue peaking in the late afternoon in MS patients.

Similar to the prevalence of fatigue, pain was experienced by the majority of the participants (80%). Regarding the prevalence, these results are in line with the findings of Davis et al. (2021) and Lopez-Leon et al. (2021) since in their studies different kinds of pain were also one of the most prevalent symptoms within long-Covid patients. However, in contrast to fatigue and sleep problems, pain was only experienced weakly in the sample with a mean score of 2,19 and with only one participant scoring higher than 4, on a scale with a maximum of 10. Moreover, these low scores are also different to the findings from the study of Lopez-Leon et al. (2021), in which they describe the experienced pain as severe incapacitating. These differences in the degree to which the pain was experienced can be mostly attributed to the small sample size of ten participants. Furthermore, among those participants that experienced pain, there were large fluctuations over the 14 days of the study but, similar to the fatigue scores, only small fluctuations over the day. These results regarding the experience of pain and the changes in sensitivity are also common in chronic pain patients (Baliki et al., 2006).

Regarding the prevalence of sleep problems within the sample, all participants experienced sleep problems at least to some degree. These findings are in line with the findings of the study by Davis et al. (2021), in which insomnia had a high estimated probability to be experienced by long-Covid patients. Moreover, like the reported fatigue and pain, there were also large fluctuations in the experienced sleep problems over the fourteen days of the study within the participants.

Concluding, the research question “How are fatigue, pain and sleep problems experienced by long-Covid patients over time?” can be answered by, that there were large differences in the extent to which the symptoms were experienced over the 14 days of the study. In contrast, over the time of the day from 8 am till 8 pm, the symptoms were experienced rather consistently, indicating that the time of the day is not relevant to symptom experience. Moreover, even though pain was experienced by the majority, the majority also experienced it only to a small degree, different to fatigue and sleep problems.

Differences in the relations between pain and sleep problems with fatigue over time between- and within participants

To answer the second research question "How are pain and sleep problems related to fatigue over time between and within long-Covid patients?" two analyses were conducted. It was found that a long-Covid patient's momentary fatigue levels are mainly related to a person's average pain level and only partially to the person's pain level at a specific time point. In the second analysis, the relation between sleep problems and fatigue was examined. This analysis showed that a long-Covid patient's momentary fatigue levels are only related to a person's average sleep problem levels and not to a person's sleep problem level at a specific time point.

In summary, for the relationship between pain and fatigue, the between-person association was stronger. This result implies that the average level of pain is stronger related to fatigue than the individual variations in pain. Therefore, the associations between pain and fatigue can be seen more on a trait-level than on state-level since the average level of pain is stronger related than the individual levels.

Moreover, the association between sleep problems and fatigue is only on a trait-level since the individual fluctuations in sleep problems were not significantly related to fatigue. Therefore, both relationships between pain and fatigue as well as between sleep problems and fatigue are not dependent on deviations in pain and sleeping problems on specific timepoints.

These findings cannot be directly compared with other research in long-Covid patients, but also not in other diseases, since the within- and between-person relationships between fatigue, pain, and sleep problems were not investigated before. Furthermore, there is also no current study that investigated the relationships of the stated variables within long-Covid patients. However, studies investigated the association between pain and fatigue, as well as the relationship between sleep problems and fatigue in patients with other diseases.

For instance, a study by Kaasa et al. (1999) found that there is a relationship between pain and fatigue in the general population. Moreover, also a more recent study by Mastaglia (2012) reported a close association between pain and fatigue. Since this study found the pain-fatigue relationship to be relatively stable over time, the results from this study can be compared to the findings from Kaasa et al. (1999) and Mastaglia (2012), even though they were not measured over time. However, a study by van Dartel et al. (2013) investigated the relationship between pain and fatigue in patients with rheumatoid arthritis (RA) over one year found similar results to this study. The study by van Dartel et al. (2013) found a relatively stable relationship between pain and fatigue in patients with RA.

Therefore, based on the results from this study, together with the knowledge of existing research, indicate that the relationship between pain and fatigue in long-Covid patients is similar to the relationship in other populations. Consequently, other findings about the relationship between pain and fatigue in other populations can perhaps be adapted to the relationship in long-Covid patients.

Furthermore, also the relationship between sleep problems and fatigue in patients with a chronic disease was investigated with a momentary assessment. For example, Stanton, Barnes and Silber (2006) reported in their study, that there is a relation between fatigue and sleep disturbances in multiple sclerosis patients. Furthermore, Ancoli-Israel et al. (2001) found that experienced fatigue is related to a disrupted sleep in cancer patients. These findings are in line with the present research and since the sleep problem-fatigue relationship was found to be time unspecific, like the pain-fatigue relationship, the momentary assessed results from previous research can be compared with the results from this longitudinal study. Nevertheless, a study by Liu et al. (2012) investigated the relationship between sleep problems and fatigue in breast cancer patients with a longitudinal study. In their study with breast cancer patients, Liu et al. (2012) found a significant association between pain and fatigue over time, similar to the results of this study in long-Covid patients.

Accordingly, like the relationship between pain and fatigue, the findings about the relationship between sleep problems and fatigue in long-Covid patients are similar to the findings about the relationship in other populations. Therefore, the findings of the sleep problem-fatigue relationship in other populations can most likely be adapted to the relationship in long-Covid patients.

The mediating effect of sleep problems on the relationship of pain and fatigue

Regarding the hypothesis that the relationship between chronic pain and fatigue is partially mediated by sleep problems a mediation analysis consisting of three LMM analyses was conducted. The results showed that there is no mediating effect of sleep problems on the relationship of pain and fatigue.

However, in the analysis, it was found that pain is related to sleep problems in long-Covid patients. This relationship was found in various populations like senior citizens (Frohnhofen, 2018), patients suffering from lower back pain (Kelly et al., 2011), but also in individuals free of chronic pain and sleep problems (Axén, 2016). Nevertheless, the relationship was not found yet in long-Covid patients.

These results implicated, that the severity of pain in long-Covid patients could be indicated by indices of sleep problems. Accordingly, the severity of sleep problems could be used as an outcome measure for the effectiveness of a pain intervention in long-Covid patients.

Strengths and Limitations

The two main strengths of this study concerning its innovativeness regarding the topic and the research method. Firstly, existing research on long-Covid symptoms was only focusing on the prevalence of the different symptoms. In contrast, this study focused for the first time on the relationships between the symptoms. This new focus on long-Covid symptoms had the aim to build a foundation on which further research can build, so possible determinants for fatigue can be found.

Secondly, this is the first study, that investigated associations over time within long-Covid patients, by assessing the data with the ESM. Previously, long-Covid studies were only using momentary assessment, which does not give insight into the fluctuations of the symptoms over time. Whereby in this longitudinal study, not only the day-to-day differences were assessed, but even the momentary differences within the day.

Furthermore, by using ESM it was possible to investigate between- and within-person differences. Moreover, the between-person differences and within-person differences for the pain-fatigue relationship and the sleep problem-fatigue relationship were never investigated before, neither within long-Covid patients nor within any other sample.

Additionally, another strength of this study is its high ecological validity, so the extent to which observed behaviour in the study can be generalized to natural behaviour (Schmuckler, 2001). Since this ESM study used a signal-contingent sampling strategy, in which the questionnaires were sent to the participants randomly within a two-hour time slot, the assessment could not be directly predicted. Therefore, the reactivity, so “the degree with which measuring operations directly affect participants’ responses provided in the momentary questionnaires” was perhaps lower than it would have been if fixed intervals would have been used (Myin-Germeys & Kuppens, 2021). In summary, the results were most likely not influenced by the measuring procedure.

However, this study also had three main limitations. Firstly, the study had a rather small sample size of N=10. The reason for the small sample size was the extensive inclusion criteria since it is highly difficult to recruit previously hospitalised long-Covid patients that

are willing to conduct a 14-day ESM study with six measures per day.

Another shortcoming arises out of one inclusion criterium namely the previous hospitalisation. There are also cases of long-Covid in non-hospitalised patients which were not taken into account and therefore there was not an ideal distribution of long-Covid patients in the sample. Moreover, the results of this study can therefore not be generalised for long-Covid patients, but only for previous hospitalized long-Covid patients.

The last main limitation of this study is, that all associations were only analysed unidirectional, so for example if the experienced sleep problems influence the experienced fatigue, but not the other way around. A bidirectional analysis would have not only validated the results but could have also added much to future research, since for example the direction between pain and sleep problems, is still poorly understood (Moldofsky, 2001).

Future research

This study found a non-time specific association between sleep problems and fatigue in long-Covid patients, so the average level of sleeping problems from an individual is related to the individual's average level of fatigue. Future research could elaborate on this finding and investigate if a decrease in sleep problems would also result in a decrease in fatigue in long-Covid patients. At the moment there is no direct treatment for fatigue. However, there are established approaches to reduce sleep problems (Friedman & Chou, 2004). For instance, a study by Côté et al. (2012) found that the treatment of sleep disorders could decrease other symptoms, such as fatigue. In their study, they treated sleep disorders, among other implications, with general sleep hygiene advice, positioning devices, weight loss, different medication such as pramipexole, and cognitive behavioural therapy (Côté et al., 2012). Future research could adapt these treatment approaches and could conduct an experimental study with long-Covid patients that suffer from fatigue and sleep problems.

Moreover, another advice for future research is to change the inclusion criteria to increase the sample size as well as the sample's diversity. It could be of great interest to broaden the focus from hospitalized long-Covid patients to all possible long-Covid patients. There are numerous cases of patients with mild Covid-19 symptoms that developed long-Covid, as well as individuals with long-Covid that have never been tested positive for Covid-19 since they have never undergone the testing procedure (Raveendran, Jayadevan & Sashidharan, 2021). Therefore, there is a high number of individuals that suffer from long-Covid, which have not been addressed so far. Conclusively, future research should focus more

on the common long-Covid symptomology during the recruitment of participants, to not miss the cases that have not been tested for Covid-19 before. However, this change could also result in the participation of individuals that suffer from the most prominent long-Covid symptoms, without being long-Covid patients. This limitation must either be accepted or the researchers have to put in the effort to test their participants for Covid-19 antibodies, which confirm a previous Covid-19 infection. Despite these shortcomings, the change in the inclusion criteria could be a way to address the unreported long-Covid cases.

Conclusion

In this ESM study, fatigue was found to be one of the most prevalent symptoms, since it was experienced by all patients and most patients had rather high fatigue scores over time, similar to previous literature (Davis et al., 2021; Lopez-Leon, 2021). In contrast, even though pain was experienced by 80% of the sample, most participants had only small pain scores over time. These results regarding the low scores of pain are contrary to the results of Davis et al. (2021) and Lopez-Leon et al. (2021), which describe pain as a severe incapacitating symptom. Similar to other studies, sleep problems were also experienced by all participants, with rather high scores over time (Davis et al., 2021). Moreover, the pain-fatigue association, as well as the sleep problems-fatigue association was found to be trait-like. Therefore, the associations are non-time specific and a long-Covid patient's momentary fatigue level is related to a person's average pain or sleep problem level and not to a person's pain or sleep problem level at a specific time point. Lastly, no supporting evidence could be found for a mediating effect of sleep problems on the relationship between pain and fatigue, indicating that an intervention against pain should also reduce experienced fatigue.

The central limitations of the study were first, the small sample size of N=10 due to the difficult inclusion criteria. Second, the focus on hospitalized long-Covid patients, even though many long-Covid patients were never hospitalized (Raveendran, Jayadevan & Sashidharan, 2021). Third, all associations were solely analysed unidirectional due to time limitations. However, a bidirectional analysis would have validated the results and would have given important insight for future research, for instance if sleep problems also influence pain, so if an intervention for sleep problems would also reduce experienced pain.

The main strengths of this study are first, its novelty, on the one hand, regarding ESM as the research method in the field of long-Covid and on the other hand, regarding the new focus on investigating associations of the symptoms, instead of purely focusing on the

prevalence of the symptoms. Secondly, by using ESM, this study was able, for the first time in the long-Covid literature, to investigate differences in the between- and within-person relationship between pain and sleep problems with fatigue.

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