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**Exploring pain-related anxiety within Long-Covid-19 patients
over time and the influential effect of sleeping problems**

- An Experience Sampling Method-study

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Abstract

Background. The SARS-CoV-2 virus evoked Long-Covid-19, marked by physical and mental complaints within infected individuals. However, few investigations have been made concerning the course and associations of prevalent symptoms of Long-Covid-19 over time by focusing on differences in symptom experience between and within people.

Objective. The current study examined the mediating effect of sleeping problems on the association between pain and anxiety within Long-Covid-19 patients over time. Moreover, the present study investigated whether experiences of anxiety, pain, and sleeping problems differ between individuals (between-person) and fluctuate for an individual within a day over time individual (within-person).

Method. The current study used the Experience Sampling Method (ESM) for 14 consecutive days among ten hospitalized Long-Covid-19 patients (Mage= 59.7 years; 50% females). State measures were assessed six times daily. The pain was assessed by four items derived from the Short-form McGill Pain Questionnaire (SF-MPQ-2). Anxiety was measured by a single item derived from the Hospital anxiety and depression scale (HADS). Sleeping problems were also assessed by a single item derived from more extensive questions.

Results. Three Linear-Mixed-Model analyses were applied. The association between pain and anxiety was found to be a strong between-person effect ($\beta = .69$, $SD = .12$, $p < .001$), however no within-person effect ($\beta = -.01$, $SD = .02$, $p = .41$). The association between pain and sleeping problems also proved to be a moderate between-person effect ($\beta = .37$, $SD = .14$, $p < .05$) and no within-person effect ($\beta = -.03$, $SD = .02$, $p < .08$). The third LMM analysis revealed a non-significant association between sleeping problems and anxiety ($\beta = .25$, $SE = .05$, $p = > .05$). Therefore, no significant mediating effect of sleeping problems on the pain-anxiety association was found.

Conclusion. Pain, anxiety, and sleeping problems were found to be mild to moderate prevalent symptoms in Long-Covid-19, which, however, differed between individuals, indicating different groups in symptom experience severity. Pain experienced from the previous day predicted night sleep problems and anxiety experiences in Long-Covid-19 patients, not found in Long-Covid-19 patients yet. Individuals differed in these symptom associations. Anxiety levels were not dependent on sleeping issues within the current sample, as identified in samples having high scores of those symptoms. Therefore, no supporting evidence for sleeping problems influencing the pain-anxiety association was found.

Introduction

In December 2019, the virus SARS-CoV-2 was detected in China, evoking the infectious CoronaVirus disease (Covid-19) (Shi, 2020). The virus has spread rapidly and is still causing a worldwide pandemic—the WHO detected Covid-19 in 223 countries (Cucinotta & Vanelli, 2020). Governments implemented enormous restrictions, such as the closure of Universities and schools and the limitation of social contact. Still, 532.201 million individuals got infected with the Coronavirus, and 6.30 million died due to their Covid-19 infection worldwide (Adams-Prassl, Boneva, Golin & Rauh, 2020; WHO, 2022a). People suffering from a Covid-19 infection are experiencing symptoms ranging from mild to severe (WHO, 2022b). Most infected individuals experience mild symptoms such as coughing, fever, and headache. However, 20% are experiencing severe symptoms, such as chest pain or shortness of breath, leading to hospitalization care (WHO, 2022b). The infection duration of Covid-19 is 2 to 14 days (Lopez-Leon et al., 2021; Raveendran, Jayadevan, & Sashidharan, 2021). However, a significant number of cases also experience symptoms beyond two weeks, experiencing Long-Covid-19 (Lopez-Leon et al., 2021). As scientific attention has been directed to the prevalence of Long-Covid-19 symptoms, however, not their association and potential interdependence, this lack of knowledge will be addressed in the current research study.

Long-Covid-19

Long-Covid-19 affects an individual physically but also psychologically. Individuals holding symptoms after a Covid-19 infection that persist beyond the 2-14 days of exposure are referred to as having "Long-Covid-19" (Lopez-Leon et al., 2021, p.3). Those individuals hold the effects of a Covid-19 infection long-term, for weeks or even months (Raveendran et al., 2021). The review study of Lopez-Leon et al. (2021) identified over 80% of individuals who had a confirmed Covid-19 infection, and symptoms continued beyond two weeks. According to Lopez-Leon et al. (2021) and Raveendran et al. (2021), the most prevalent and persisting symptoms of Long-Covid-19 are fatigue, acute distress symptoms, joint, headache, and chest pain. Additionally, according to Chen, Haupert, Zimmermann, Shi, Fritsche, and Mukherjee (2022), the prevalence of those symptoms is higher in Long-Covid-19 patients who have been hospitalized compared to those who have not been hospitalized. Individuals suffering from Long-Covid-19 experience severe consequences such as job loss, decreased daily functioning, decreased wellbeing, and a general impairment in life quality (Raveendran et al., 2021).

Moreover, detected psychiatric disorders based on a Covid-19 infection are anxiety disorders, insomnia, or dementia (Lopez-Leon et al., 2021). However, there is still a considerable lack of research concerning Long-Covid-19 and how the physical and psychological symptoms are associated or interdependent in individuals with Long-Covid-19.

Pain-related anxiety

As Lopez-Leon et al. (2021) and Aiyegbusi et al. (2021) reviewed, pain and anxiety experiences are highly prevalent symptoms of Long-Covid-19. According to Chaturvedi (2020), the development of anxiety is the most associated emotional response when experiencing pain. Carleton et al. (2009) and McCracken and Gross (1998) explained this phenomenon by stating that individuals experiencing pain interpret their bodily sensations as maladaptive. Anxiety responses can be catastrophizing and helpless (Carleton et al., 2009). The belief that the perceived pain is harmful and the evoked stress reaction increases the chances of developing an anxiety disorder (Carleton et al., 2009; Gorji et al., 2014). McCracken & Gross (1998) conceptualized the cognitive, behavioral, and physical response of anxiety when experiencing pain and pain events as "pain-related anxiety" (p. 180). The disabilities such as distress, tiredness, or a weaker immune system deriving from pain-related anxiety are sometimes more substantial than the pain experience (Chaturvedi, 2020; McCracken & Gross, 1998). Therefore, pain-related anxiety contributes to developing and maintaining pain perception, worsening it, and evoking the mentioned symptoms besides pain and anxiety (Chaturvedi, 2020; McCracken & Gross, 1998). As pain and anxiety were identified as prevalent symptoms of Long-Covid-19 (Lopez-Leon et al., 2021), Long-Covid-19 patients might also experience pain-related anxiety.

Limited knowledge is available of pain-related anxiety; few existing research studies focus mainly on chronic pain patients. A longitudinal study by Hanegem et al. (2022) revealed that chronic pain patients are associated with negative affect, including anxiety-related effects, emphasizing an association between pain and anxiety over time. Moreover, the longitudinal research study of Castillo et al. (2013) revealed that experiencing pain evokes intense anxiety in individuals experiencing pain. Even if some studies investigated the association longitudinal, no current study investigated the association within Long-Covid-19 patients over time. Also, Matthews, Deary, and Whiteman (2003) emphasized the importance of conducting momentary longitudinal assessments for taking the different facets and changes of constructs into account to gain detailed insights. Despite evidence about the fluctuating and individual perceived nature of

pain and anxiety, few existing research studies focused on the association between pain and anxiety longitudinal and none among Long-Covid-19 patients differentiated in symptom variance. Furthermore, no current research determined symptom experience among individuals and how the course of pain-related anxiety varies within Long-Covid-19 patients.

Hadjistavropoulos, Asmundson, and Kowalyk (2004) stated that there are differences in experiencing pain-related anxiety, as some individuals hold a greater anxiety sensitivity than others. This implies that the experience of pain-related anxiety varies between individuals. Moreover, pain and anxiety perception is not perceived as stable over time, nor is the course of intensity and severity (Aiyegbusi et al., 2021; Bennett, 2012; Mols et al., 2018). It can be assumed that the experience of pain-related anxiety varies from situation to situation and daily for an individual. Therefore, the symptom experience and association between pain and anxiety might differ between Long-Covid-19 patients experiencing pain-related anxiety and within a Long-Covid-19 patient.

The influence of sleeping problems on pain-related anxiety

Aiyegbusi et al. (2021) reported that a common symptom of Long-Covid19 is sleeping burdens such as insomnia. Additionally, Orrù et al., 2021 stated that troublesome sleep had been especially identified in people who suffered from a Covid-19 infection or held Long-Covid-19 compared to people who did not get infected. Sleep is a crucial part of everyday life and an individual's physical and psychological well-being (Chokroverty, 2010). A lack of sleep or a decrease in sleep quality can have severe adverse effects and causes mental and physical disorders (Aiyegbusi et al., 2021). Sleep deprivation can be identified as insomnia, which is conceptualized as having intense troublesome sleep over time, meaning lacking the ability to fall asleep, stay asleep by waking up multiple times at night, and having a hard time falling asleep again.

Sleep significantly affects other physical and emotional states, such as pain and anxiety. Many existing research studies focused on a reciprocal assessment of the association between pain, anxiety, and sleeping problems. In a study by Sayar, Arikan & Yontem (2002), it was found that both anxiety and pain correlate positively with sleep deprivation, meaning that pain and anxiety predict sleeping problems. Additionally, Moffitt et al. (1991) implied that experiencing pain results in lousy sleep. In turn, according to Lopez-Leon et al. (2021), sleep deprivation can cause psychiatric problems such as severe anxiety. Moreover, although sleeping problems proved

to be influential for affective states, sleeping problems have been identified as a prevalent symptom of Long-Covid-19 (Lopez-Leon et al., 2021).

There are just a few existing research studies investigating whether sleeping problems account for the association between pain and anxiety, indicating a significant effect of sleeping problems on pain-related anxiety. One research study by Diaz-Piedra et al. (2014) assessed the mediating effect of sleep quality on the association between pain and emotional responses such as anxiety within chronic pain patients. They argued that sleep quality fully mediates the association between pain and anxiety, accounting for its effect. Furthermore, Miró et al. (2011) found a mediating effect on sleep quality, thereby arguing that pain does not account for anxiety self-standing, arguing for a full mediation. Therefore, even if Diaz-Piedra et al. (2014) and Miró et al. (2011) found that sleep fully mediates the association between pain and anxiety.

However, one-time retrospective assessments were implemented for all existing research studies concerning a mediation effect of sleeping problems on pain-related anxiety. As mentioned above, this dismisses the fluctuating, constantly changing nature of sleeping problems, pain, and anxiety over time (Kaur & Bhoday, 2017; Hadjistavropoulos et al., 2004; Matthews, Deary, & Whiteman, 2003). Therefore, multiple momentary assessments of pain, anxiety, and sleeping problems should be implemented to assess fluctuations over time within a person, but also to assess differences between Long-Covid-19 patients.

Present study

Although pain, anxiety, and sleeping problems are identified as prevalent Long-Covid-19 symptoms (Lopez-Leon et al., 2021; Aiyegbusi et al., 2021), no research study focused on a potential association between symptoms. Past research already identified that sleeping problems account for the pain-anxiety association. However, research was conducted in a one-time retrospective, thereby dismissing the fluctuating nature and constantly changing nature of pain, anxiety, and sleeping problems (Aiyegbusi et al., 2021; Bennett, 2012; Mols, Schoormans, de High, Oerlemans & Husson, 2018). Therefore, no current research could assess whether fluctuations within a person in those symptom associations over time and whether individuals differ in those responses. Therefore, greater insight and more accurate results can be obtained by assessing a potential mediating effect of sleep problems on the pain-anxiety association longitudinal, differentiating within and between persons. This provides awareness and novel insight, benefiting the individualization of existing health care interventions for the best possible

treatment. Therefore, the current research study investigates to what extent the association of pain-related anxiety is mediated by sleeping problems within Long-Covid-19 patients over time (Figure 1). The present research will use the Experience Sampling Method (ESM), capturing the fluctuating and dynamic nature of stress, pain, and anxiety (Myin-Germeys & Kuppens, 2021).

Based on the gathered information, four research questions have been investigated:

RQ1: "To what extent is pain associated with anxiety over time in Long-Covid-19 patients?"
It is expected that pain is positively associated with anxiety over time within Long-Covid-19 patients. Moreover, it is expected that the association is a within-and between subject association.

RQ2: "To what extent is pain associated with sleep problems in Long-Covid-19 patients over time?"
It is expected that pain is positively associated with sleeping problems over time in Long-Covid-19 patients. Moreover, it is expected that the association is a within-and between-subject association.

RQ3: "To what extent are sleeping problems associated with anxiety in Long-Covid-19 patients over time?"
It is expected that sleeping problems are associated with anxiety over time in Long-Covid-19 patients. Moreover, it is expected that the association is a within-and between-subject association.

RQ4: "To what extent is the association between pain and anxiety mediated by sleep problems over time in Long-Covid-19 patients?"
It is expected that there is a mediating effect of sleep problems on pain-related anxiety over time in Long-Covid-19 patients.
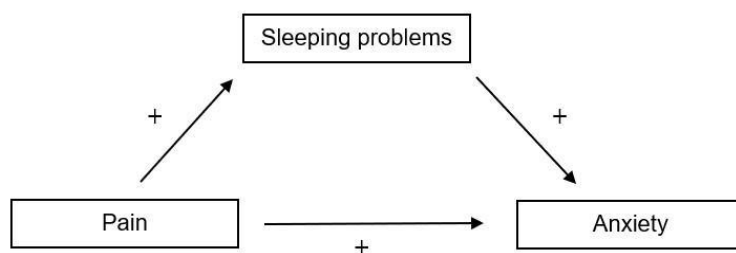
Figure 1. Mediation model of sleeping problems on the pain-anxiety association.

Methods

The current study is a supplementary study of an ongoing cohort study from the hospitals Medisch Spectrum Twente (MST) in Enschede and Ziekenhuis Groep Twente (ZGT) in Almelo and Hengelo. Patients dismissed from hospitalization between September 2020 and February 2021 filled out a questionnaire three months, six months, nine months, and twelve months after discharge.

Design

The current study used the longitudinal Experience Sampling Method (ESM), conceptualized as a self-report diary method, assessing an individual's real-life experiences in their naturalistic environment by implementing multiple daily assessments (Myin-Germeys & Kuppens, 2021). By capturing real-life states, recall biases by relying on long-term memories will be avoided, ensuring reliable outcomes and ecological validity (Van Berkel, Ferreira & Kostakos, 2017; Csikszentmihalyi, 2014). Moreover, capturing individuals' affective states multiple times per day over time allows for assessing fluctuations within a construct. The experience of pain, anxiety, and sleeping problems differ from situation to situation and from day to day (Bennett, 2012; Mols, Schoormans, de High, Oerlemans & Husson, 2018). Therefore, multiple assessments per individual over time through the ESM results in more accurate results and greater insight into the symptom variance within a person and also differences between Long-Covid-19 patients (Fisher et al., 2018).

Data were collected from September 1 until November 5, 2021, using the Ethicadata application on participants' smartphone devices (Ethicadata, 2020). The Behavioural, Management, and Social Sciences Ethics Committee of the University of Twente approved the study in May 2021.

Participants

People who were hospitalized with Covid-19 and discharged from the hospital at least three months ago stated that they felt significantly better (N=16) or worse (N=12) one year after their hospitalization were recruited for an interview study to get insights into their current health condition. The criterion for selection for participating in the ESM was worsening their general health conditions compared to one year before. Therefore the 16 participants who stated that they experienced a decrease in health status were invited to participate in the ESM study, and 11 participants enrolled. One participant was excluded from participation due to missing the set response rate of a minimum of 30% of all measurements. Finally, a sample of N=10 matched the criteria and was selected for the current ESM study.

The current sample holds an age range from 48 to 76, with an average age of 59.7 years (SD = 7.65). Five participants identified themselves as female and five as male (n=5, 50%).

Materials and measures

The study was part of more extensive research, thus, also containing questionnaires concerning 17 other Long-Covid-19 symptoms. However, only the measurements of troublesome sleep, anxiety, and pain were used for the intended purpose of the current study. To prevent participant burden, a maximum of two minutes per assessment was implemented to complete the questionnaire. Data was collected using the application Ethicadata, which is especially applicable for self-report questionnaire studies (Ethicadata, 2020). The application allows for capturing participants' behavior continuously, assessing their momentary state, thereby providing within-and between person fluctuations (Ethicadata, 2020).

The questionnaire consisted of two parts, a retrospective daily one-time assessment of sleeping problems and six momentary state assessments per day of anxiety and pain. Items used were derived from the 21 items state questionnaire and were answered with a Likert scale or the Visual Analog Scale (VAS) (Appendix). All questions were derived from validated questionnaires. Pain items are derived from the Short-form McGill Pain Questionnaire (SFMPQ-2) (Kahl &Cleland, 2005; Melzack, 1987). Four items assessed the pain variable. Firstly, participants were asked whether they experience current pain or not ("Yes" or "No"). If they answered "Yes," three questions concerning the specificity of pain experience followed, including headache ("To what extent do you currently have a headache?"), joint pain ("To what extent do you currently have joint pain?") and chest pain ("To what extent do you currently have

chest pain/discomfort?"). Participants needed to identify their pain score on a scale from 0, meaning no pain, to 10, representing worst pain. Sleeping problems were assessed by the item "To what extent did you have trouble sleeping at night?", derived from more extended questions from Brys, Stifft, Bossola, Gambaro, and Lenaert (2020) and Jean, Sibon, Husky, Couffinhal, and Swendsen (2020). Participants needed to identify their sleep from 1 (had no trouble sleeping) to 5 (I had a lot of trouble sleeping last night). The item measuring anxiety was derived from the Hospital anxiety and depression scale (HADS) (Pallant & Tennant, 2007). Anxiety was assessed by the question "Right now I feel anxious," where participants had to choose between strongly disagree (1) to strongly agree (7).

Based on the assumption of Lopez-Leon et al. (2021) that headache, joint pain, and chest pain are the most prevalent pain symptoms within Long-Covid-19 patients, a partial correlation analysis by controlling for overall timepoints was conducted for the three pain variables chest pain, headache, and joint pain. According to Adamson and Prion (2013), scales used in clinical settings should have a minimum Cronbach's alpha of .70 for being assessed as excellent and internally consistent. The correlation analysis of headache and chest pain and Cronbach's alpha ($r_{headache\&chestpain}$ = .83; α =.89) proved excellent internal consistencies within the current sample, therefore, headache and chest pain were united to an overall pain variable.

Procedure

A pilot test by the researchers and a student having Long-Covid-19 symptoms have been conducted. Participants needed to sign an informed consent before getting interviewed. Based on that, they were asked whether they would like to join the ESM study, where they again had to sign a within-application informed consent provided in Ethicadata before starting the study. Due to different interview dates, participants began the ESM study after the interviews at other time points.

One day before the start of the study, participants received an identical survey from practicing with the set-up of the application. A signal-contingent sampling strategy was implemented, where data was randomly collected within predetermined time intervals (8 a.m. until 10 a.m., 10 a.m. until 12 p.m., 12 p.m. until 2 p.m., et cetera, up until 8 p.m.) for six times a day for 14 consecutive days resulting in 84 state measurements. Sleep quality was assessed once a day in the morning from 8 a.m. until 12 p.m. Hektner et al. (2007) stated that after one week of

assessment, a sample is representative, while after 14 days, the quality declines. Also, five to eight measurements ensure optimal results (Klasnja et al., 2008).

Data analysis

The data was exported from Ethicadata into SPSS 27.0 for statistical analysis. Participants who did not complete the assessment (response rate < 30%) were excluded from the analysis. The dataset was put into a long format.

For the pain variables headache, chest pain, and the united pain variable, values were coded as 0 if pain experience was subjectively assessed as "No." Afterward, a lagged variable (lag= -6) for all six consecutive assessments of the total pain score examination days was generated. The first assessment day was not included as no lagged variable was available. Through the lagged variable, associations could be estimated, as night sleep problems were just assessed once a day. The pain scores of the previous day were associated with the night's sleep and anxiety level on the next day. As the ESM consists of multiple assessments, it allows for between-and within-person analysis, capturing inter-and intra individual variations. For this purpose, person-mean (PM) scores and person mean-centered (PMC) scores of the lagged pain variable and sleeping problems were computed. PM scores reveal the average level of pain and sleeping problems across all time points, allowing for between-person analysis. In contrast, PMC scores capture momentary deviations in pain and sleeping problems per time point by identifying to what extent momentary deviations differ from the individual's PM score, allowing for within-person analysis.

Due to a data collection of 14 consecutive days, the chance of missing an assessment was increased (Myin-Germeys et al., 2021). Moreover, since multiple assessments per person were conducted, the current state data holds interdependence. Therefore the Linear-Mixed-Model (LMM) analysis was implemented, accounting for a significant amount of missing data and interdependence of data points (Myin-Germeys et al., 2021). LMMs with first-order autoregressive (A1) repeated covariance type, and repeated timepoints measures were implemented to assess the mediating effect of sleeping problems on the pain-anxiety association over time. For the analysis, all scores were standardized, resulting in the usage of standardized estimates for all analyses, allowing for the comparison of different variable scores derived from different scales. Furthermore, descriptive statistics of the raw scores of the variables were assessed to get insight into participants' states by considering means and standard deviations

(SD). Additionally, line graphs were created to illustrate an individual's fluctuations and associations between anxiety, pain, and sleeping problems over the assessment period (Curran & Bauer, 2011).

The mediation analysis was conducted using the method of Baron and Kenny (1986):

(1) For assessing the overall association between pain and anxiety, an LMM analysis was implemented with anxiety as the outcome variable and the lagged pain variable as the fixed covariate. To clarify the within and/or between-subject associations, another LMM was conducted by treating anxiety as the outcome variable and the PM and PMC scores of the lagged pain variable as the fixed covariates.

(2) For assessing the overall association between pain and sleeping problems, an LMM analysis was implemented with sleeping problems as the outcome variable and the lagged pain variable as the fixed covariate. For assessing whether the association between pain and sleeping problems is a within and/or between-subject association, an LMM analysis was conducted by treating sleeping problems as the outcome variable and the PM and PMC scores of the lagged pain variable as the fixed covariates

(3) For assessing whether sleeping problems are associated with anxiety, an LMM analysis was implemented with anxiety as the outcome variable and sleeping problems as the fixed covariate. For clarifying whether the association between sleeping problems and anxiety is a within-or between-subject design, another LMM was, setting it as a fixed covariate, as well as the PM and PMC score of sleeping problems. Anxiety was treated as an outcome variable.

(4) For assessing the mediating effect of sleeping problems an LMM was conducted, with the lagged variable of pain and sleeping problems as fixed covariates, and anxiety as the outcome variable.

Results

In total, 1.820 measurements were taken, 84 state measurements for perceived pain and anxiety and 14 for sleeping problems, resulting in 182 measurements per participant. Participants responded on average to 62 out of 98 prompts, reflecting a response rate of 60.8% (SD = 20%, range = 31%-92%). Descriptive statistics, including means, SD, and the minimum and maximum scores for anxiety, sleeping problems, and the individual, as well as the combined pain scores, are displayed in Table 1.

Table 1. *Minimum, maximum, means, and standard deviations (SD) for the raw state measures in the final sample (N=10).*

Variable	Minimum (minimum scale score)	Maximum (maximum scale score)	Mean (SD)
Pain Total	0 (0)	8 (10)	1.73 (2.33)
Chest pain	0 (0)	8 (10)	1.57 (2.15)
Headache	0 (0)	8 (10)	1.90 (2.72)
Anxiety	1 (0)	7 (7)	2.77 (1.87)
Sleeping problems	1 (1)	5 (5)	2.17 (.98)

Description of pain, anxiety, and sleeping problems in Long-Covid-19 patients

In Figures 2 to 6, participants' mean scores for pain, anxiety, and sleeping problems are displayed for six-time points per study day and all days of the assessment period. Between- and within-person variability and deviations of pain, anxiety, and sleeping problems during the study period are visualized, indicating that participants tend to have fluctuating affective states, which also differ between persons and within persons. Generally, it can be observed that the current sample of Long-Covid-19 patients holds substantial small to moderate fluctuations for both within- and between-persons.

Description of pain

In Figure 2, fluctuations of mean pain responses within and between persons are displayed for the 6-time slots per day. All participants seemed to be almost consistent and stable in experiencing pain within an assessment day. Responses varied within a range of +/- 1 point on the pain scale for 5 participants. The morning pain scores were almost similar to the mid-day and evening pain scores. The pain intensity can also be identified as low, except for participants 7 and

3, who display moderate to high pain scores. However, 5 participants perceived no pain at all time points within one assessment day (participants 1, 5, 6, 8, and 9).

As visualized in Figure 3, pain experiences of Long-Covid-19 patients assessed daily for two weeks display more significant variability in pain scores compared to considering pain scores within a day. However, fluctuations are small-ranged of -/+ 2 points. Within this range, small changes in pain scores can be observed, indicating a small within-person variability in pain scores over the study period. Moreover, differences in experienced pain intensity can be observed between participants. While participants 7 and 3 displayed moderate to high pain intensity, some experienced mild pain symptoms, while half of the participants again experienced no pain during the overall assessment period.

Therefore, within the current sample, considering the graphical illustration of the assessment of pain scores within a day and for all days over the assessment period, small-ranged within-person. However, more significant between-person fluctuation can be observed for 5 participants.
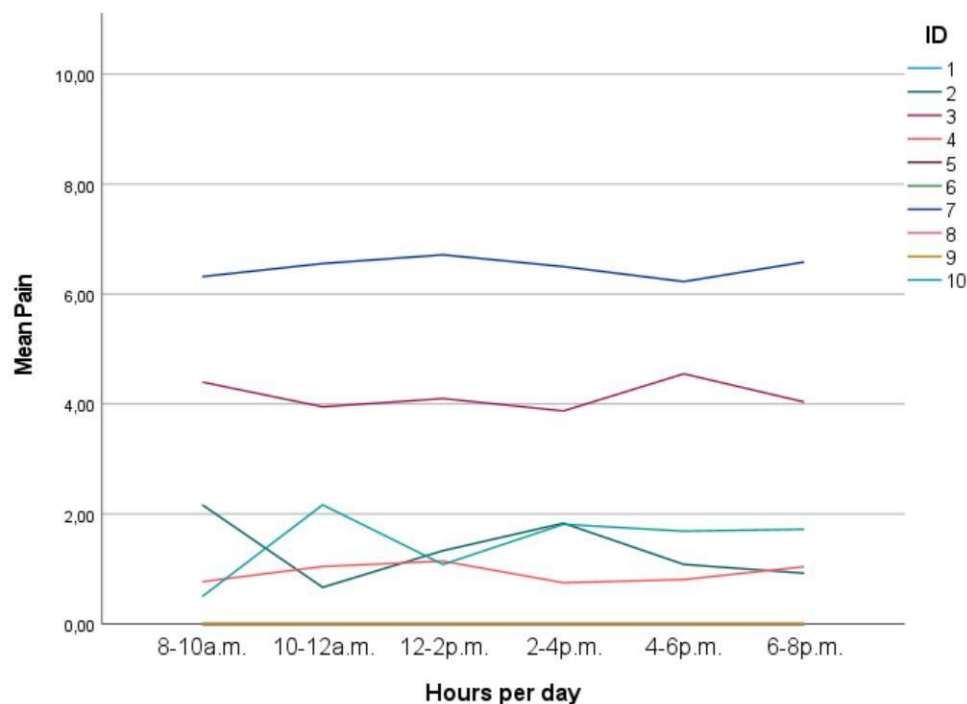

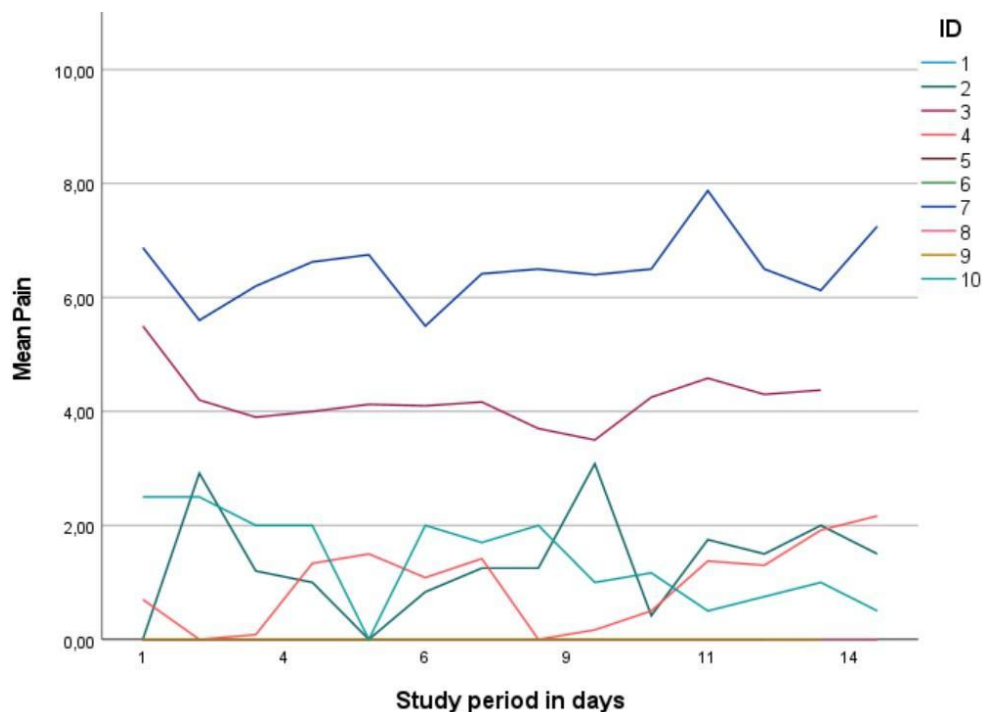**Figure 2:** *Mean pain score per participant per time-point during the total study period.*

Figure 3: *Mean pain score per participant per day during the total study period.*

Description of anxiety

In Figure 4, fluctuations of mean anxiety experiences within and between persons are displayed over the assessments within a day. Within an assessment day, anxiety scores can be assessed as fairly consistent within individuals, holding rather small-ranged changes of +/-1 point. The morning pain scores were almost consistent with the mid-day and evening pain scores. Participant 8 displays the most significant within-person effect by having a change of anxiety during 12 and 2p.m, however small-ranged. Participants 3 and 7 displayed the highest anxiety scores compared to other individuals, as most of the other participants scored within a range from 2 to 4. However, three participants perceived no anxiety on all assessments (2, 9, and 10).

In Figure 5, substantial between-and within-person anxiety fluctuations are visualized for the total assessment period in days. Almost all participants experienced different anxiety intensities and variations daily within the assessment period, ranging within +/-2 anxiety points. Participant 4 displayed the most notable within-person variability, whereas 3 participants experienced no anxiety during the whole assessment period. Therefore, small-ranged within-person fluctuations of anxiety scores within the current sample for seven participants can be observed, however, with greater visibility of between-person differences.
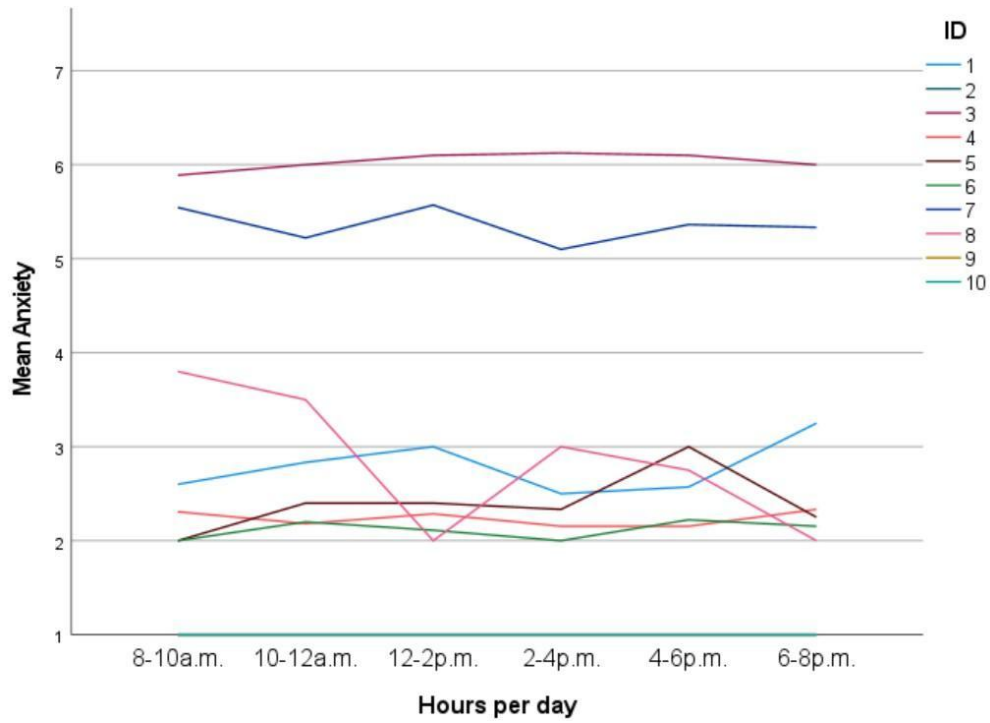
Figure 4: *Mean anxiety score per participant per time-point during the total study period.*
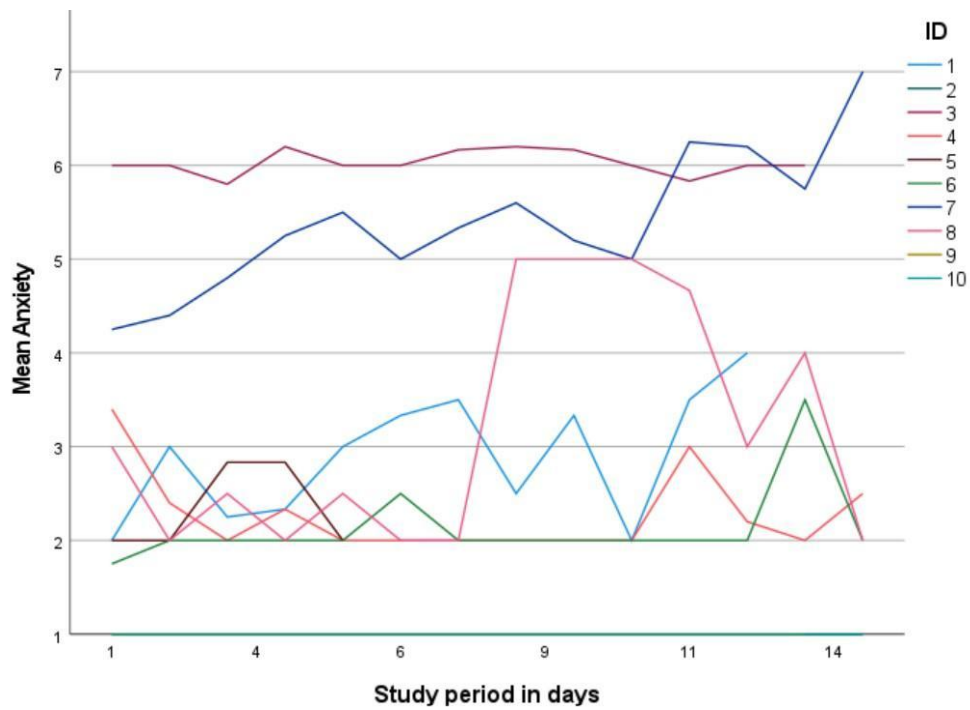

Figure 5: *Mean anxiety score per participant per day during the total study period.*

Description of sleeping problems

In Figure 6, fluctuations of sleeping problems within and between persons having Long-Covid-19 are displayed for the whole study period. All participants experienced sleeping problems to a certain extent. For most participants, significant within-person variability can be portrayed, especially for participants 2 and 10, displaying sleep problem scores ranging from a minimum of 1 (no trouble sleeping) to a maximum of 5 (much trouble sleeping). Furthermore, apparent differences between participants can be observed. Participants differed in whether they experienced troublesome sleep during the assessment period and to what extent. For some, a higher intensity of sleeping problems can be observed on a particular day than for other individuals. Moreover, some individuals experienced a greater intensity of sleeping problems than others, such as participant 2, who experienced more severe sleeping problems over time than participant 4. For the current sample, significant within-person fluctuations in sleeping problems can be identified. However, also between-person differences are visible.
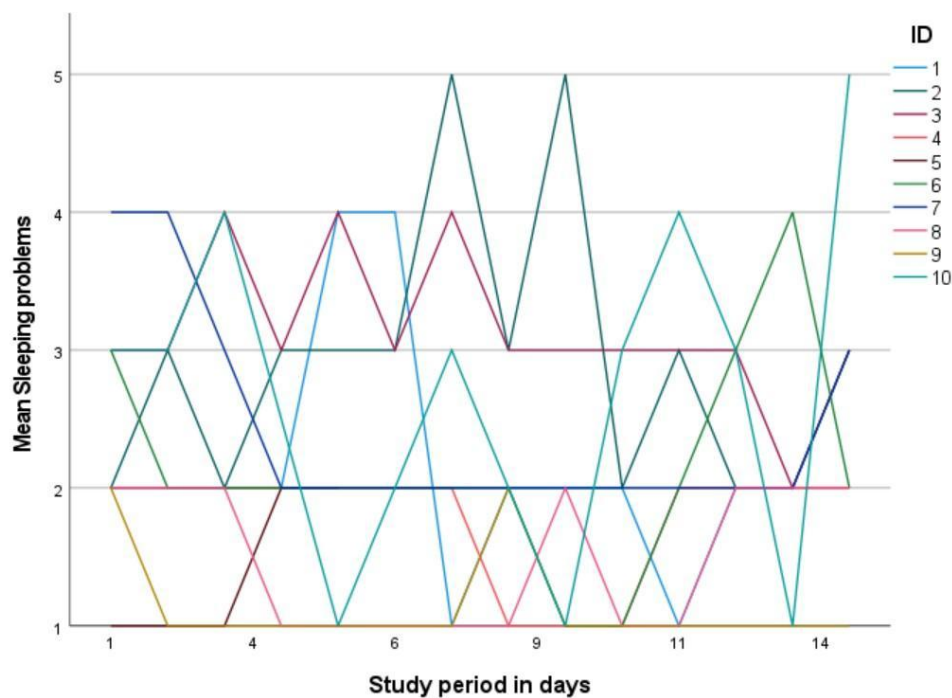

Figure 6: *Mean sleeping problems score per participant per day during the total study period.*

Association between pain and anxiety within Long-Covid-19 patients

For an overall momentary association covering all time points, LMM analysis revealed a non-significant association of pain and subsequent anxiety ($\beta = -.02$, $SE = .03$, $p = >.05$). Figure

7 displays the depicted overall non-significant association between the constructs for the current sample of Long-Covid-19 patients.
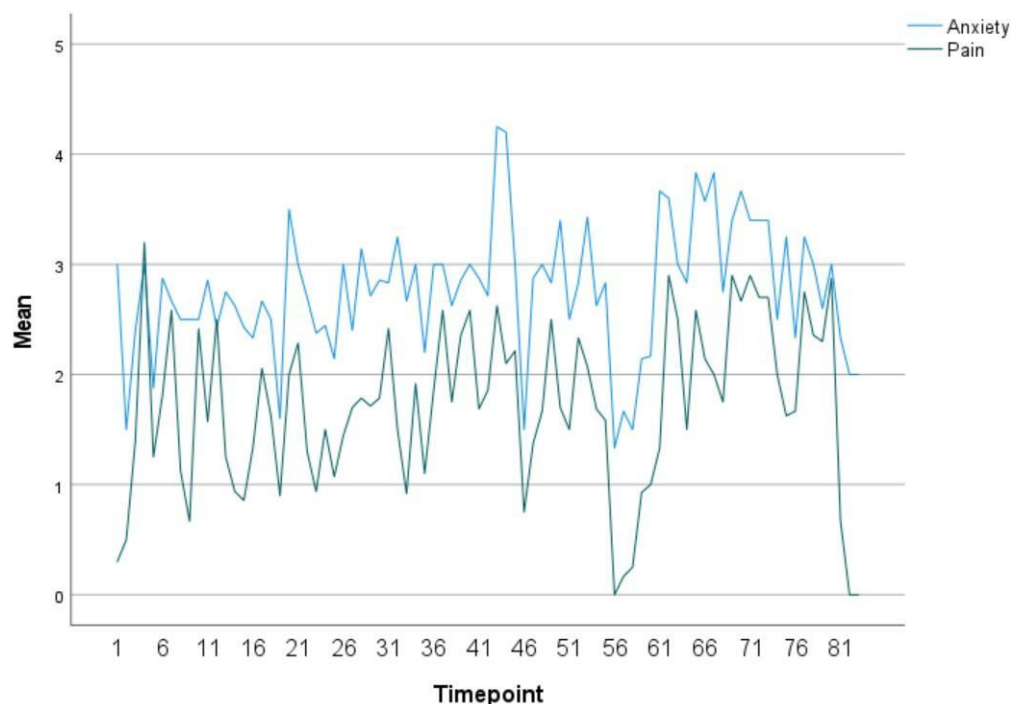

Figure 7: *Mean scores of pain and anxiety scores of the sample during the total assessment period, ranging from timepoint 1 to 84.*

The association of pain and anxiety within and between individuals

Furthermore, it was examined whether anxiety depends on perceived pain at a specific time point or on an average pain level of patients having Long-Covid-19. The analysis proved that the PM score of the lagged pain variable significantly predicted anxiety, assuming a strong and positive between-person association between anxiety and pain on the previous day. The PMC lagged pain score proved to be not significantly associated with anxiety (Table 2).

Table 2. *The within-and between person associations between pain on the previous day and anxiety.*

	Estimate (β)	Std. Error	df	t	Sig.	Confidence interval
PM Pain	.69	.12	18.71	6.25	<.001	.46-.93
PMC Pain	-.01	.02	313.33	-.82	.41	-.04-.02

The association between pain and sleeping problems within Long-Covid-19 patients

The second LMM investigated the association between perceived pain and perceived sleeping problems covering all time points in individuals having Long-Covid. The association between the lagged pain score and subsequent sleeping problems proved to be non-significant (β = -.04, *SE* = .03, *p* = >.05). Figure 8 visualizes the overall non-association of pain and sleeping within Long-Covid-19 patients.
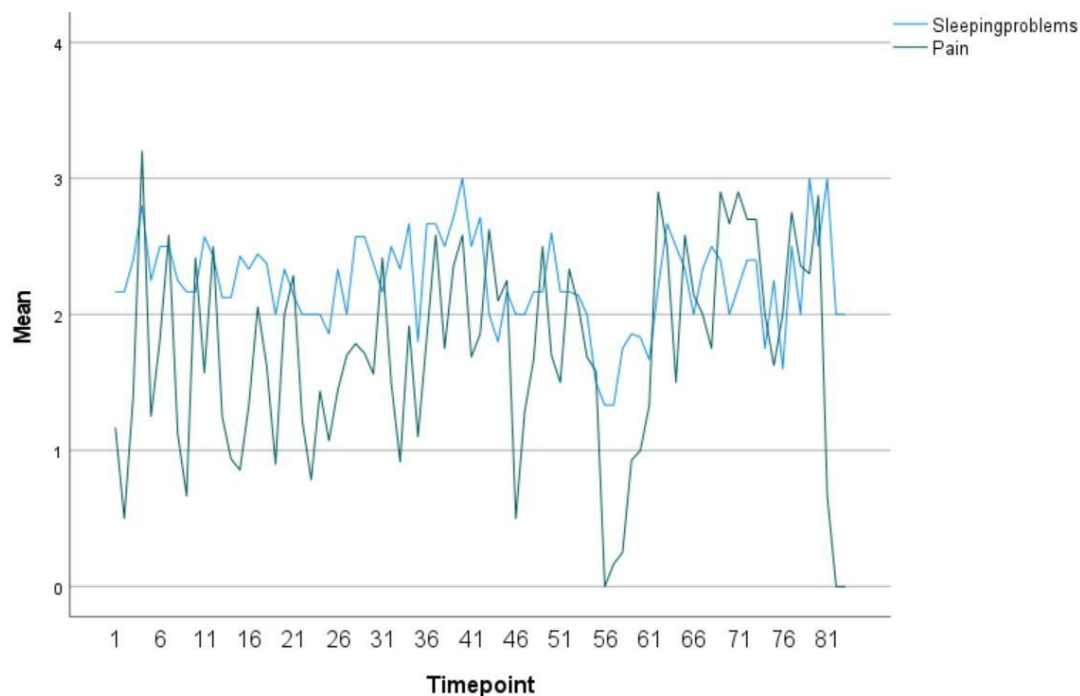

Figure 8: *Mean scores of pain and sleeping problems score of the sample during the total assessment period, ranging from timepoint 1 to 84.*

The association of pain and sleeping problems within and between individuals

Furthermore, it was examined whether sleeping problems depended on perceived pain at a specific time or on the average pain level of patients with Long-Covid-19. The analysis proved that the PM score of the lagged pain variable significantly predicted sleeping problems, revealing a moderate and positive between-person association. However, the PMC score proved to be non-significant, indicating a non-significant within-person association in the current sample of Long-Covid-19 patients (Table 3).

Table 3. *The between (PM) and within (PMC) person effects of the association between pain and sleeping problems.*

	Estimate (β)	Std. Error	df	t	Sig.	Confidence interval
PM Pain	.37	.14	20.99	2.54	<.05	.07-.67
PMC Pain	-.03	.02	441.76	-1.74	.08	-.06- -.01

The association of sleeping problems and anxiety within and between individuals

The third LMM investigated the association between sleeping problems and anxiety within Long-Covid-19 patients. The overall association proved to be non-significant ($\beta = .25$, *SE* = .05, *p* = >.05). The PMC score of sleeping problems ($\beta = .27$, *SE* = .20, *p* = >.05), as well as the PM score ($\beta = .12$, *SE* = .04, *p* = >.05) were non-significant for the sleeping problems- anxiety association. Therefore, neither a between-person nor a within-person association between sleeping problems and anxiety can be observed within the current sample. Figure 9 visualizes the findings, portraying the non-association.
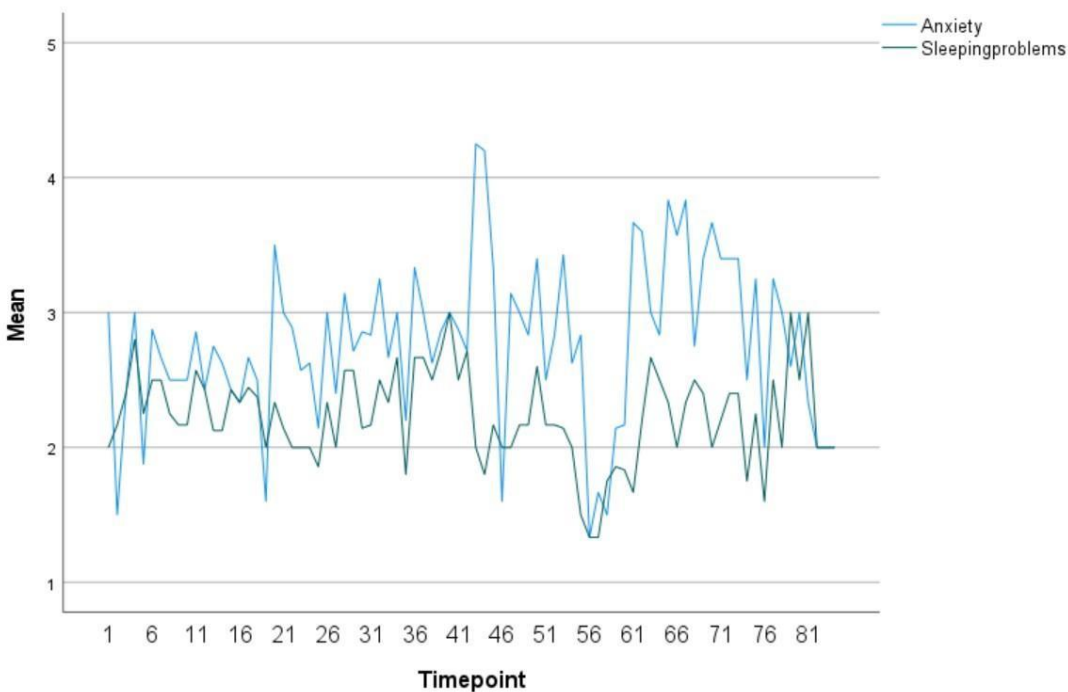

Figure 9: *Mean of sleeping problems and anxiety score of the sample during the total assessment period, ranging from timepoint 1 to 84.*

The mediating effect of sleeping problems on the relations between pain and anxiety in LongCovid patients

The fourth LMM investigated sleeping problems as a mediating variable in the pain anxiety association in Long-Covid-19 patients covering all timepoints. After the association between sleeping problems and anxiety proved to be non-significant (β = .25, SE = .05, p = >.05), sleeping problems cannot be considered a mediator in the association between pain and anxiety (Barron & Kenny, 1986).

Discussion

The current research study aimed to assess whether pain and anxiety are associated in Long-Covid-19 patients over time and whether sleeping problems are mediating the pain-anxiety association. Moreover, the purpose was to clarify whether the investigated associations can be considered trait-like and state-like momentary effects. The current findings proved that the association between pain and anxiety, as well as between pain and sleeping problems, are related to a Long-Covid-19 patient's average pain level and not to a person's pain level at a specific time. Moreover, no supporting evidence was found that there is an association between sleeping problems and anxiety among Long-Covid-19 patients. Therefore, sleeping problems cannot be considered a mediator in the pain-anxiety association within the current sample (Barron & Kenny, 1986).

Out of the current sample of Long-Covid-19 patients, 5 out of 10 (50%) experienced some extent of pain, 7 out of 10 (70%) experienced anxiety, and 8 out of 10 (80%) Long-Covid-19 patients experienced sleeping problems over time. Comparing the prevalence of these symptoms to existing literature concerning Long-Covid-19 symptom prevalence, the review of Lopez-Leon et al. (2020) and Huang et al. (2021) identified pain, anxiety, and sleeping problems as the most common and highly prevalent symptoms within Long-Covid-19 patients. The indicated prevalence percentages of pain, anxiety and sleeping problems were higher in the current sample compared to Lopez-Leon et al. (2020); however, the sample size for assessing the prevalence of those three symptoms was significantly greater in their review study. Long-Covid patients experienced severe or moderate symptoms within the current sample over two weeks. Others experienced no symptoms over the total assessment period, which is against the expected significant prevalence of pain, anxiety, and sleeping problems. Smith and Haythornthwaite (2004) and Axén (2016) argue that patients who experience pain more constantly are used to the pain

experience, therefore experiencing lower intensities of symptoms, compared to patients having acute momentary pain, which might explain the low response scores. Moreover, the individual differences between the participants emphasize a considerable variability among persons' symptom experiences. This finding coincided with the results of existing research studies, which identified symptom variance between individuals (Hadjistavropoulos et al., 2004; Mathews et al., 2003).

To answer the first research question, namely that pain and anxiety are associated in Long-Covid-19 patients over time, supporting evidence was found that the association between pain and anxiety is a strong trait-like effect. However, there is no state-like momentary effect. Therefore, a Long-Covid-19 patient's momentary anxiety levels are related to a person's average pain level and not to that person's pain level at a specific time point, suggesting that a relatively consistent and continuous experience of pain evokes anxiety within Long-Covid-19 patients. Supporting, the current findings displayed that pain and anxiety responses were relatively stable over time, indicating that the currently assessed Long-Covid-19 patients approximately experience the same level of pain and anxiety over the assessment period. A trait-like association between pain and anxiety was already indicated by Hadjistavropoulos et al. (2003), however, within chronic pain patients. Furthermore, pain and anxiety levels of the Long-Covid-19 patients proved to be averagely mild within the current sample. Also, some individuals experience no pain and anxiety at all. Michaelides and Zis (2019) explained that high pain and anxiety levels are primarily associated with individuals having a severe acute pain experience, not with patients holding relatively constant experiences of the symptom association. Although symptoms are perceived as mild, continuous pain symptoms evoke anxiety responses (Knaster et al., 2012; Jensen & McFarland, 1993; Estlander, Karlsson, Kaprio, & Kalso, 2012) found within the current sample. The recent findings also align with existing longitudinal research studies in chronic pain patients, indicating pain-related anxiety (Castillo et al., 2013; Hanegem. Et al., 2013).

Answering the second research question, namely that pain experiences are associated with sleeping problems over time within Long-Covid-19 patients, the current research found supporting evidence that the association between pain and sleeping problems is a trait-like effect and no momentary state-like effect. An individual's sleeping problems are dependent on a person's average pain level and not on momentary states of experienced pain. Therefore, relatively constant pain experiences from the previous day result in sleeping problems in Long-Covid-19 patients rather than fluctuating pain states. Supportingly, Moffitt et al. (1991)

found that pain experiences lead to sleep deprivation. Moreover, differences between Long-Covid-19 patients were identified, with some individuals having no pain levels or sleep disturbances during the assessment period and some having more severe symptom experiences, supporting the current finding of differences in symptom variance between individuals. Moreover, according to Axén (2016), the degree of sleeping problems depends on the intensity of the pain experience, explaining the currently found moderate association, as both pain and sleeping problems are identified as being averagely low within the current sample of Long-Covid-19 patients. However, as 5 out of 10 patients experienced no pain during the assessment period, the moderate association could be due to the non-experience of sleeping problems, pain, and anxiety in some Long-Covid-19 patients.

To answer the third research question, that sleeping problems are associated with anxiety over time, and no supporting evidence was found that sleeping problems are associated with anxiety within the current sample of Long-Covid-19 patients. A study with chronic pain patients by Menefee et al. (2000) found that the greater the severity of sleeping problems, the greater the experienced anxiety. Morin, Gibson & Wade (1998) also said poor chronic pain sleepers would report more severe anxiety responses. Supprtingly, Macey et al. (2010) stated that the association between sleeping problems and anxiety has only been found for high scores of sleep problems and anxiety levels. On average, considering the current findings, the severity of experienced perceived sleeping problems within Long-Covid-19 patients is assessed as averagely low, as well as anxiety perception, which might explain the depicted non-association between sleeping problems and anxiety. Additionally, previous research studies have investigated the association, indicating that, in turn, sleeping problems are dependent on anxiety levels (Gerrits et al., 2015; Lerman et al., 2015), suggesting that there is an association between sleeping problems and anxiety, however having a different dependency than assessed in the current research study.

Lastly, due to the non-association between sleeping problems and anxiety, no mediating effect of sleeping problems within Long-Covid-19 patients on the pain-anxiety association was found. The results can only be compared to the research study of Diaz-Piedra et al. (2014), who also investigated the same mediation analysis within chronic pain patients. Diaz-Piedra et al. (2014) found a mediating effect of sleeping problems on the pain-anxiety associations. Therefore, the results of the current research study are not in line with the findings of DiazPiedra et al. (2014). However, they investigated subjective sleep quality, not sleeping problems. Therefore the comparison should be made with caution as sleep quality also includes other factors of sleep

(Krystal & Edinger, 2008). Compared to the current sample, sleep disturbances and anxiety levels in the chronic pain population of Diaz-Piedra et al. (2014) were among the most prevalent symptoms. Chronic pain severity and the arising functional disability are decisive for developing sleep disturbances and anxiety. As within the current sample, just some individuals experienced symptoms at all, also relatively mild, which might lead to the non-influence of sleeping problems on the pain-anxiety association.

Although the symptom experience seems relatively mild within the current sample, continuous pain perception of a person predicts sleeping problems at night and anxiety levels within the next day for Long-Covid-19 patients. Menefee et al. (2000) supported the recent finding by stating that pain can be considered the baseline construct and that sleeping problems and pain are predictive of mood disorders such as anxiety. However, other research studies found that pain and sleeping problems can also depend on anxiety (Gerrits et al., 2015; Lerman et al., 2015), suggesting a reciprocal association between those symptoms (Moldofsky, 2001; Alvaro, Roberts, & Harris, 2013). As sleeping problems did not influence pain-related anxiety, associations were found in the current and previously conducted research studies (O'Brien et al., 2010). Different mechanisms instead of a mediation model or other unidirectional or even bidirectional dependencies might underlie pain, anxiety, and sleeping problems within Long-Covid-19 patients.

Strengths and Limitations

First, research concerning physical and emotional disturbances arising and persisting due to a Covid-19 infection is limited due to its novelty. Existing research investigating LongCovid-19 focused on the prevalence of symptoms, not on their associations, whether they depict interdependence, and whether they differ within and between individuals. Therefore, the current research provided novel insights by investigating and thereby providing new information concerning the association of prevalent Long-Covid-19 symptoms, pain, anxiety, and sleeping problems,

Another significant and outstanding strength of the current research was investigating the association between pain, anxiety, and sleeping problems as a mediating factor using the ESM. No previous research investigated those associations over time within Long-Covid19 patients. Furthermore, investigating those associations using the ESM allows for new insight into between-subjects and within-subjects effects. The current research study demonstrated the

importance of investigating fluctuating and time-varying constructs such as pain, anxiety, and sleeping problems over time. Thereby, it was revealed that there are differences between and within individuals concerning subjective symptom perception. Moreover, using ESM prevents recall bias due to real-time assessment, leading to great ecological validity (Conner & Lehmann, 2012), allowing for representative results of the actual daily life of Long-Covid-19 patients (Myin-Germeys & Kuppens, 2021). Furthermore, the current research study holds an excellent compliance rate for ex-hospitalized individuals still experiencing symptoms, leading to great insight into the experiences of Long-Covid-19 patients.

The associations have been investigated unidirectional due to time limitations. However, several research studies argue the importance of assessing those associations bidirectionally, as they hold interdependence. The current research study, however, also contains shortcomings. (Menefee, Cohen, Anderson, Doghramji, Frank & Lee, 2000; Moldofsky, 2001; Alvaro, Roberts, & Harris, 2013). Moreover, pain symptoms were combined; however, assessing them separately within Long-covid-19 patients by also including more pain-specific prevalent constructs, such as joint pain, could provide more significant insights into which pain symptom seems to be most prevalent in the association with sleeping problems and anxiety. Furthermore, according to Knaster et al. (2012), health-related anxiety reactions should be assessed more in-depth by specifying anxiety reactions as they differ widely in also tackling them in therapy.

Moreover, the sample size of the current research study was relatively small, with N=10. A greater sample size could generate richer insights and the generalization of the current findings. In addition, as the present analysis was performed on a group level, conducting N=1 studies could be interesting for gaining more detailed insight into individual symptom association. Moreover, participants from the current study were hospitalized, while individuals with mild Covid-19 symptoms also develop Long-Covid-19 and should therefore also be considered. The last shortcoming was technical errors in Ethics Data, resulting in participants not receiving their daily state questionnaire on the fourteenth day, leading to missing data points.

Further research

Generally, ESM research should aim at assessing prevalent symptoms and their association in Long-Covid-19 patients to get a broader insight into their dependency. Some associations proved to be non-significant. However, further research could include confounding variables, which were not considered in the current research. For instance, according to Özlü, Öztürk,

Karaman, Tekin, and Gür (2021), when individuals engage in relaxation exercises such as progressive muscle relaxation within Covid-19 patients improves sleep quality and anxiety, leading to a non-association. Moreover, high standard deviations, graphical illustrations, and the findings of the LMM revealed individual differences in pain-, anxiety-, and sleeping problems perception. Focusing on individuals with higher symptom perception might lead to more significant associations of pain, anxiety, and sleeping problems. Further research could create sub-groups of Long-Covid-19 patients, differentiating between individuals experiencing mild and more severe symptoms.

Further research could focus on the investigation of Long-Covid-19 symptoms over time, as investigating associations on a state level by multiple assessments might gain richer insights into the course of symptoms by also preventing recall biases such as in one-time retrospective assessments (Matthews, Deary, &Whiteman, 2003). Moreover, the current study showed differences between patients' symptom experiences. Therefore, further research should investigate the benefit of existing health care interventions for creating individually adapted help, ensuring the best possible outcome for Long-Covid-19 patients.

Moreover, further research should assess the reciprocal symptom associations, as the associations between pain, sleep problems, and anxiety proved to be bidirectional in many research studies (Moldofsky, 2001; Alvaro, Roberts, & Harris, 2013). Understanding the interplay of Long-Covid-19 symptoms benefits existing health care interventions, as knowledge of symptom dependencies in Long-Covid-19 patients is limited. Moreover, other studies underlined the importance of differentiating anxiety reactions when individuals experience pain-related anxiety differently as they are approached in therapy (Hadjistavropoulos et al., 2004). For instance, when pain-related anxiety is experienced, catastrophizing the bodily sensation could be a possible instant reaction and repressing the symptoms. Therefore, those different maladaptive coping patterns of how individuals experience anxiety need to be specified within questionnaires for Long-Covid-19 patients to ensure fitting help.

Conclusion

This ESM study found that pain, anxiety, and sleeping problems are prevalent and not very severe symptoms within Long-Covid-19 patients over time. A relatively small variability in symptom experience within a Long-Covid-19 patient over two weeks was visible. Pain experiences evoked night sleeping problems and anxiety the next day, which differed between

Long-Covid-19 patients. Moreover, sleeping problems and anxiety levels depend on a relatively consistent and continuous pain experience in Long-Covid-19 patients. However, no supporting evidence of the association between sleeping problems and anxiety and the mediating effect of sleeping problems on the pain-anxiety association was found within Long-Covid-19 patients during the assessment period.

Shortcomings of the current sample are a small sample size, restricting a great generalization and detailed insight into the associations investigated. Moreover, the present research was limited to hospitalized patients and was conducted on a group level. Also, the association was assessed one-directional, while others reported a reciprocal association of pain, anxiety, and sleeping problems. Lastly, technical Errors of the application "Ethicadata" lead to data loss. However, the outstanding strength of the current research study is the investigation of associations between prevalent Long-Covid-19 symptoms, which was not investigated in yet, leading to novel insights. Moreover, using the ESM allows capturing behavior and emotional states within participants' naturalistic environment, ensuring ecological validity. Moreover, through multiple assessments over time, the study found differences between persons' symptom perceptions and associations, providing differentiation between Long-Covid-19 patients' symptom experiences.

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Appendix

Sleeping problems

1. To what extent did you have trouble sleeping last night?

   - 1 had no trouble - 5 had a lot of trouble SAQ

State pain

1. To what extent do you currently have a headache? '0' means no headache, '10' means worst headache.
2. To what extent do you currently have joint pain? '0' means no joint pain, '10' means worst joint pain.
3. To what extent do you currently have chest pain/discomfort? '0' means no chest pain, '10' means worst chest pain.

State anxiety

1. Right now I feel anxious.

   1 Strongly disagree – 7 Strongly agree SAQ