Brain Fog and Depressed Mood in the Daily Life of People with Post-COVID after Hospital Discharge:

An Experience Sampling Study

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Abstract

Background. The COVID-19 virus has left many people with physical and psychological post-COVID complaints such as brain fog and depressed mood. However, there is only limited knowledge available about the course of and possible correlations between the two symptoms over time due to it being a relatively novel field of research. **Objective.** The subjective experience of brain fog and depressed mood was explored. In addition, the relationship between the two variables was examined to see if there is any association between the two variables and, if applicable, on which level this association acts, on a state-like level or a trait-like level. Lastly, it was investigated if the variables predicted each other approximately two hours later. **Method.** For this study, the Experience Sampling Method (ESM) was used in order to collect repeated momentary self-reports six times a day for 14 consecutive days. Brain fog and depressed mood were measured via the Ethica app among ten Dutch people with post-COVID symptoms after hospital discharge (M_{age} = 59.7, 50% female, 50% male). To analyze the longitudinal relationship between brain fog and depressed mood, Linear Mixed Models (LMM) were conducted. **Results.** Depressed mood and brain fog were experienced moderately and continuously in patients with post-COVID. Moderate and positive associations were found between brain fog and depressed mood (β=.45; p <.001), significant at both the between-person (trait-like) level (β =.56; p <.001) and within-person (state-like) level (β=.11; p <.001). However, no significant results were found when checking if the variables predicted each other approximately two hours later. **Conclusion.** Depressed mood and brain fog as post-COVID symptoms should be taken seriously since they were found to be experienced moderately and continuously. There was an association between these two symptoms, which acted mainly on a trait-like level and only little on a state-like level. Meaning that people with (more or less) depressed mood were more likely to experience (more or less) brain fog than others. However, the individual was only a bit more likely to experience (more or less) brain fog when experiencing (more or less) depressed mood than they usually did. It was also found that depressed mood did not predict brain fog two hours later, and neither did brain fog predict depressed mood two hours later. This study is the first study examining depressed mood and brain fog among post-COVID patients in a longitudinal design and distinguishing between the state- and trait-like level. This can be used to enhance the treatment of post-COVID patients and contribute to the knowledge about this relatively unknown disease.

Keywords: post-COVID, depressed mood, brain fog, experience sampling method

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Brain Fog and Depressed Mood in the Daily Life of People with Post-COVID after Hospital Discharge: An Experience Sampling Study

The outbreak of Coronavirus Disease in 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), still impacts millions of people physically and psychologically. The virus was first reported in late December 2019 in Wuhan, China (Wu et al., 2020). One month later first cases in Europe were reported (Nadeau et al., 2021). In the Netherlands, over 8 million people have been infected with the virus, and the number of deaths has reached over 20 thousand since 2020 (World Health Organization, 2020). When infected with COVID-19, influenza-like symptoms are typical, such as high temperature, sore throat, headache, cough, fatigue, diarrhea and muscle or joint pain (Struyf et al., 2022). In addition, the loss of sense of smell and taste is considered a red flag for diagnosing the presence of COVID-19. Usually, a mild COVID-19 infection lasts around seven to ten days after the onset of symptoms, while severe infections can take up to 20 days (Rhee et al., 2021). Still, even after recovering from the virus, many people reported a continuously worsened life quality compared to before infection with the COVID-19 virus. The so-called post-COVID syndrome (former: long-COVID) refers to impairments in various aspects of physical and mental health at least three months after a COVID-19 infection (Soriano et al., 2021). Since this field is not yet researched in depth, it is essential further to investigate the symptoms of post-COVID and possible correlations. Therefore, this study aims to explore depressed mood and brain fog in post-COVID to provide insights on impacts of the disease in daily life.

Post-COVID

According to the WHO clinical case definition working group, post-COVID is defined as a condition that "occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis" (Soriano et al. 2021, p.e105). Due to the novelty of post-COVID, the literature about concrete numbers is still limited. However, one study reported an incidence rate of 30% infected with post-COVID after a COVID-19 infection (Logue et al., 2021). Another study from Italy found that 87% of COVID-19 hospitalized patients showed at least one persistent symptom after 60 days. One-third of the participants had one or two symptoms, whereas the majority showed three or more (Carfì & Landi, 2020). The reported prevalence of residual symptoms is about 30% in patients

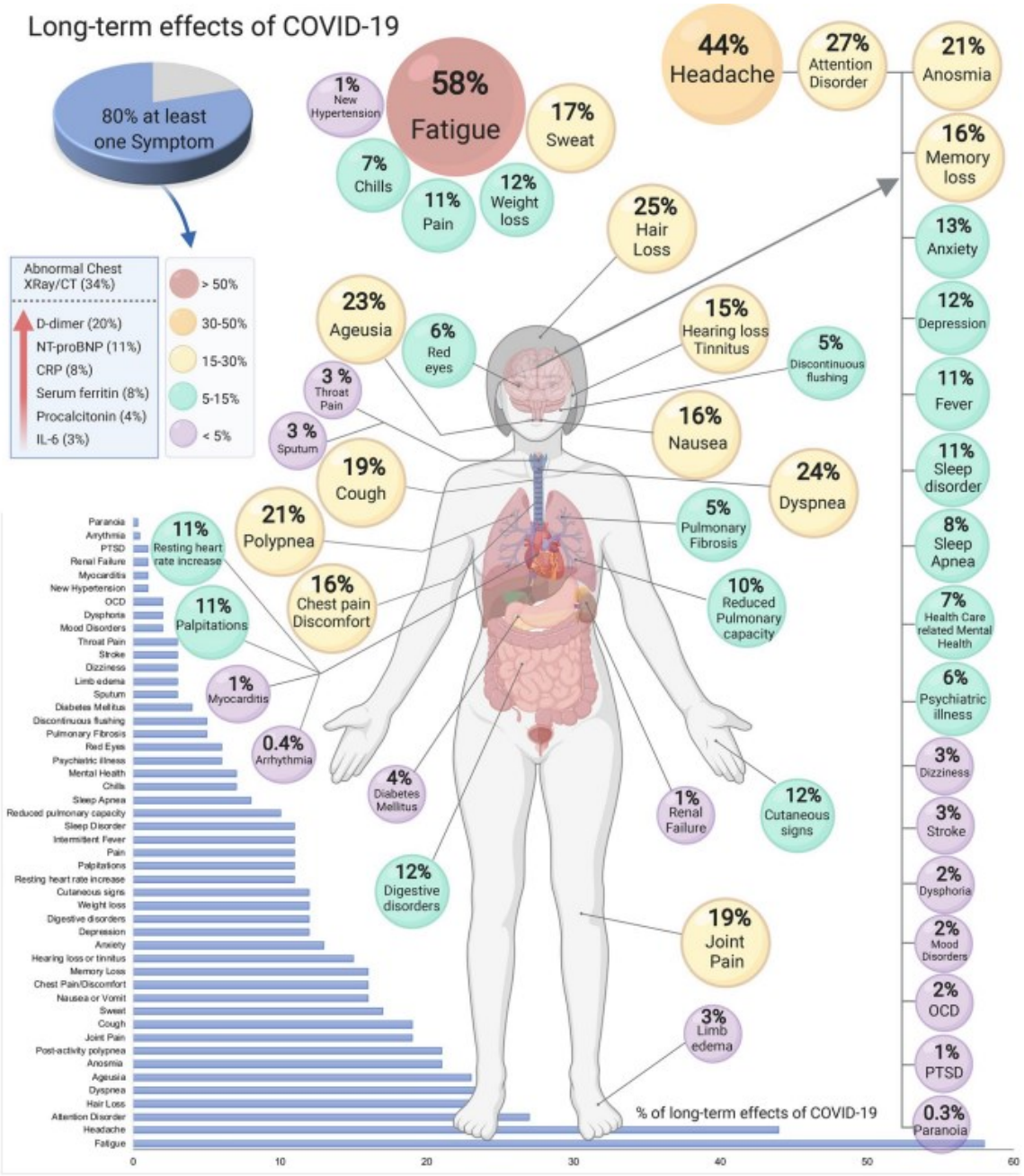
treated on an outpatient basis and around 80% among patients treated in hospitals (Carfì & Landi, 2020; Tenforde et al., 2020).

Lopez-Leon et al. (2021) conducted an extensive systematic review and meta-analysis of studies among people with COVID-19 infection, including over 40 thousand patients. In this analysis, over 50 long-term effects of COVID-19 were found, underlining the immense consequences COVID-19 can have on mental and physical health (See Figure 1). Salamanna et al. (2021), who also conducted a systematic review, stated that post-COVID symptoms are not only present in severe COVID-19 cases but also in mild and moderate ones. This would increase the total cases of post-COVID since not only people with a severe course of COVID-19 are left with long-term consequences.

It seems like a COVID-19 infection may have long-term effects on a wide range of organs. These include physical and mental long-term symptoms, such as shortness of breath, fatigue, cognitive dysfunction and a widespread impact on everyday functioning. Similar findings were found by Fernández-de-las-Peñas et al. (2021), who described the different systems influenced by post-COVID in more depth. One important system, the neurocognitive system, is also affected by symptoms like brain fog, dizziness, loss of attention and confusion when infected with post-COVID.

Figure 1

Reported Symptoms of Post-COVID



Note. From ‘‘More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis,’’ by S. Lopez-Leon et al., 2021, *Scientific Reports, 11*(1), p. 9 (https://doi.org/10.1101/2021.01.27.21250617).

Post-COVID and Brain Fog

COVID-19’s potential to damage the brain has been mentioned in various lines of literature. Neurological manifestations like febrile seizures, encephalitis and convulsions or central nervous system involvement like inflammation and demyelination have been reported

in a wide range of studies (Asadi-Pooya & Simani, 2020). However, some long-term effects on the brain caused by COVID-19 may be more subtle. For example, the inability to concentrate, memorize or pay attention is also correlated with post-COVID syndrome. These symptoms belong to an occurrence commonly known as “brain fog”. Brain fog is an already-known phenomenon, occurring in various illnesses like fibromyalgia, hypothyroidism, chronic fatigue syndrome, Lyme disease and more (Kravitz & Katz, 2014; Samuels & Bernstein, 2022; Ocon, 2013; Roos, 2021). Ross et al. (2013) described brain fog as having difficulties in focusing, thinking and communicating, being forgetful and/ or cloudy. Wilson (2008) emphasizes the importance of investigating brain fog since it contributes to problems in daily life, low self-esteem, unhappy relationships, accidents, and even delinquency and crime since brain fog can lead to frustration and inability to function well in society. He lists various common causes for brain fog, like illnesses and chronic infections, psychological causes like mental and emotional conflicts, unresolved traumas and more.

There are multiple theories on the etiology of brain fog as part of post-COVID. Asadi-Pooya et al. (2022) hypothesized that the risk for brain fog increases when experiencing a more severe course of COVID-19 because of a stronger immune response, harm caused by drastic medical treatment and brain regions (e.g., cingulate cortex) affected when infected with COVID-19. Research from the last two years suggests that severe cases of COVID-19 are caused by the immune system producing excessive inflammatory proteins named cytokines (Krishnan et al., 2022). Therefore, post-COVID is regarded as a consequence of a prolonged, exaggerated immune response, also called a cytokine storm. This mechanism has the potential to cross the blood-brain barrier, which affects cognition. Other disorders like sepsis, autoinflammatory disorders and primary and secondary hemophagocytic lymphohistiocytosis (HLH) are also caused by cytokine storms. (Fajgenbaum and June, 2020).

In a study investigating brain fog, over 65% of people with post-COVID reported brain fog as a symptom at least six months post-viral infection (Jennings et al., 2022). According to Krishnan et al. (2022), millions of individuals with post-COVID report brain fog among their top three symptoms. To gain more insight into the course of brain fog, it would be necessary to investigate which situations in daily life are impacted by brain fog in patients with post-COVID and how it persists during the day. It was found that brain fog fluctuates for some patients with postural tachycardia syndrome during the day, with which the severity of brain fog was depicted as highest in the morning (Ross et al., 2013). Even though the reported incidence rate of brain fog among post-COVID patients varies between the studies, it is

essential to acknowledge the phenomenon more in the scientific community since subjective well-being is significantly lower among patients with brain fog. More specifically, it was found that among patients with post-COVID experiencing brain fog is associated with stress, anxiety and depressed mood (Orfei et al., 2022).

Post-COVID and Depressed Mood

Next to brain fog, a worsening of mental health is correlated with post-COVID. Issues that came along with COVID-19, like decreased social contacts, economic consequences, hospitalization and quarantine, can impact mental health negatively (Saltzman et al., 2020). Fernández-de-las-Peñas et al. (2021) named psychological complaints related to post-COVID, like post-traumatic stress disorder, anxiety, depression and insomnia. According to the review of Lopez-Leon et al. (2021), every tenth person with post-COVID shows depressed mood as a symptom, while others report higher numbers, up to 40% of people with depressive symptoms like depressed mood (Kamal et al., 2021; Lorkiewicz & Waskiewicz, 2021).

Since post-COVID is a relatively new phenomenon, the course of depressed mood among post-COVID patients over time has not been researched yet. Nevertheless, it would be beneficial to examine the course of depressed mood to see whether it indeed fluctuates, as an experience sampling study conducted among young adults by Mehlan (2021) suggested. Additionally, Rossi and Rossi (1977), who also studied mood patterns in young adults from the United States, found that men and women experience mostly negative mood at the beginning of the week and more positive mood towards the weekend. Thus, to be able to treat depressed mood in post-COVID patients, it is necessary to assess whether it is indeed bound to a pattern, such as mood patterns related to weekdays. On the other hand, Schouten (2021) examined mood in an experience-sampling study with cancer patients, in which it was shown that mood fluctuates over time even though no clear diurnal pattern could be found.

As stated in the article of Saltzman et al. (2020), symptoms of depression and other serious mental illnesses are common after pandemics and other disasters. Especially patients who need to be hospitalized or have problems maintaining social contact because of their post-COVID symptoms can be more at risk for developing psychiatric disorders since social contact and support are perceived as essential factors of mental health. Furthermore, an association was found between poor mental health and social isolation due to hospitalization (Saltzman et al., 2020). Next to social isolation, uncertainty about the future, survivor guilt and broad exposure to media may also induce a depressed mood after infection with COVID-19 (Mazza et al., 2022).

Depressed Mood and Brain Fog in Post-COVID Patients

Depressed mood and brain fog are co-occurring symptoms in various illnesses, including post-COVID (Brown & O'Brien, 2021; Reinfeld, 2022). It seems intuitive that mood influences how efficiently our thought processes proceed. In line with this assumption, a survey by Ettleson et al. (2021) demonstrated that hypothyroidism patients who experience brain fog also often experience depressed mood. Still, to our knowledge, no differentiation was made between if the patients who have, on average more (or less) depressed mood are also experiencing more (or less) brain fog or if patients who experience more (or less) depressed mood than they usually do then also experience more (or less) brain fog. A distinction between those two levels would be necessary to include not only overall insights into post-COVID patients but also individual differences and avoid errors of inference (Myin-Germeys & Kuppers, 2021; Curran & Bauer, 2011). Furthermore, Cristillo et al. (2022) found a significant correlation between brain fog and self-rated depressive symptoms in patients with post-COVID one year after hospital discharge, concluding depressive symptoms as the strongest predictor of persistent brain fog. Still, this study did not examine this association over time, they checked cognitive complaints twice in a follow-up, respectively six months apart, and depressive symptoms were measured only at the second measurement. In this regard, Cristillo et al. (2022) suggest more extensive longitudinal studies to shed further light on possible underlying mechanisms. For this, continuous measurement of depressed mood and brain fog would be suitable.

There is also the possibility that brain fog influences mood in a negative way, as Miskowiak et al. (2021) suggest. More cognitive impairments may create more depressed mood in daily life due to difficulties in overcoming cognitive challenges. They suggest that the observed association between cognitive impairment and depressive symptoms could be bi-directional. Since both symptoms have not been researched yet as predictors of each other among patients with post-COVID, this study will concentrate on the association between depressed mood and brain fog, if they are associated more on a state-like level or trait-like level, and if those two symptoms are predicting each other over time. For this, a longitudinal and extensive examination of brain fog and depressed mood would suit.

Experience Sampling Method

"Taking a single snapshot is usually not the best approach to understand the whole movie. Yet, this is what we most commonly do in mental health research and practice" (Myin-Germeys & Kuppers, 2021, p.7). So far, much research concerning post-COVID has used retrospective cross-sectional surveys or other retrospective methods (Shanbehzadeh et al.,

2021). By assessing symptoms, mood or behavior in retrospect, risks include recall and memory biases. Both diminish the validity of measurements and should be avoided (Myin-Germeys & Kuppers, 2021). In addition, the variables of interest are only measured once in cross-sectional designs. Fluctuations remain undetected, and the course of symptoms, behaviors, feelings etc., during the day remain unknown. Therefore, possible associations between variables over time cannot be determined. Especially in this study, investigating symptoms and mood variations due to post-COVID is crucial to assess the daily course of the disease. Another limitation of the cross-sectional design is the separation of between-person and within-person associations. While the between-person analysis gives more of an overall insight into how individuals differ from one another, the within-person analysis gives more insight into the daily experiences within one individual and how these can differ and fluctuate depending on context or time (Myin-Germeys & Kuppens, 2021). Including only one level limits understanding the true nature of the association between two variables (Curran & Bauer, 2011).

To overcome these limitations of cross-sectional designs, a longitudinal measurement design seems most suitable to assess the daily impact of post-COVID. The various fluctuations of symptoms, behavior and emotions of post-COVID can be assessed in more depth and over a more extended time. To additionally include the fluctuations during the day and different levels of associations, the Experience Sampling Method (ESM) is more insightful (Conner & Lehman, 2012). ESM has been developed to track those experiences in real-time, in a real-world setting, using self-reports tracking context and exact momentary experiences multiple times per day (Myin-Germeys & Kuppens, 2021). These multiple measurement points throughout the day allow in-depth insight into the fluctuations over a prolonged time. Another advantage is the possibility of differentiating between the within-person and between-person levels. ESM offers this more substantiated information by measuring the participant multiple times throughout the day (Myin-Germeys & Kuppens, 2021).

In sum, to detect possible associations between the variables of interest, real-life assessments at multiple time points per day are of advantage. Since this study focuses on brain fog and depressed mood, this measurement technique could offer a more in-depth insight into the symptoms of post-COVID compared to previous cross-sectional designs. Finally, with knowledge obtained from this study, treatment options and interventions can be better targeted for post-COVID patients.

Aim of the Study

Since post-COVID is a relatively new phenomenon, examining the different symptoms more in-depth for both clinical services and research is essential. Should brain fog and depressed mood be correlated or predict one another, long-term treatment and rehabilitation options could be adjusted, and possibly contribute to reduce the pandemic´s socioeconomic and long-term health burden. For example, if brain fog plays a role in inducing depressed mood in post-COVID patients, treatment for brain fog could also reduce depressed mood in post-COVID patients. Krishnan et al. (2022) found that when facing brain fog as a symptom, a multi-pronged approach should be advocated, including focusing on sleep and nutrition. Furthermore, exploring the association between brain fog and depression could help the patients suffering from post-COVID themselves by understanding the disease more and the possible connections between their symptoms. In sum, the goal of this study is an in-depth examination of the relationship between brain fog and depressed mood.

Taking together, post-COVID should be researched in an exploratory and longitudinal investigation due to the relatively novel field of research and unknown associations between the variables of interest. This study aims to investigate the relationship between brain fog and depressed mood in post-COVID patients six months after hospital discharge. More specifically, first, the experience of depressed mood and brain fog over time in patients with post-COVID is examined. Then, the association between brain fog and depressed mood is investigated. Finally, more in-depth knowledge about the association between the variables of interest will be obtained and can be used to help patients suffering from post-COVID by understanding the different levels of the association and possible predictions of associations over time between the different symptoms. Based on the previous paragraphs, the following research questions (RQ) were formulated:

Research Question 1: *How are brain fog and depressed mood subjectively experienced over time in Dutch people with post-COVID six months after hospital discharge?*

Research Question 2: *Is there an association between depressed mood and brain fog in Dutch people with post-COVID six months after hospital discharge?*

Research Question 3: *What is the between-person and within-person association between brain fog and depressed mood in Dutch people with post-COVID six months after hospital discharge?*

Research Question 4: *Does depressed mood predict brain fog over time in Dutch people with post-COVID six months after hospital discharge?*

Research Question 5: *Does brain fog predict depressed mood over time in Dutch people with post-COVID six months after hospital discharge?*

RQ four and five are exploratory to gain insight about a possible causal relationship between depressed mood and brain fog.

Methods

This ESM study was derived from an ongoing longitudinal cohort study on health after hospitalization caused by COVID-19 infections, investigating long-term consequences. The participants of this complementary study were treated in the Medisch Spectrum Twente (MST) hospital in Enschede. After discharge, they were invited to fill in a survey five times over the course of one year; immediately after discharge, after three months, six months, nine months and twelve months. From the cohort study, the participants of this ESM study were selected and investigated six times a day over two weeks.

Participants

For further investigations, participants were recruited via purposive selection using 3-month data from the cohort study. 42 patients discharged after being hospitalized with acute COVID-19 were selected based on self-reported health change compared to prior to the COVID-19 infection with the Dutch SF-36 (Aaronson et al., 1998). With a score of 50 or higher, the participants indicated that they recovered, while a score of <25 indicated that they did not. Based on this test, 32 participants who indicated a worsening of their health status and ten who reported improvement were invited to participate in an interview study. Eventually, 16 non-recovered and eight recovered patients participated in the interview study and gave information about their current health status. After the interview, the 16 participants who reported deteriorated health were asked to participate in the current ESM study, of which 11 enrolled.

There were four inclusion criteria concerning the ESM study, namely the participants needed to be (1) discharged from the hospital after a COVID-19 infection confirmed by a PCR test, (2) at least 18 years or older, (3) proficient in Dutch for the surveys and interviews and (4) having symptoms attributed (primarily) to post-COVID. In addition, the required compliance rate of 30% or more of the ESM surveys needed to be met (Delespaul, 1995). This ESM study used and analyzed the remaining data of ten participants (N= 10).

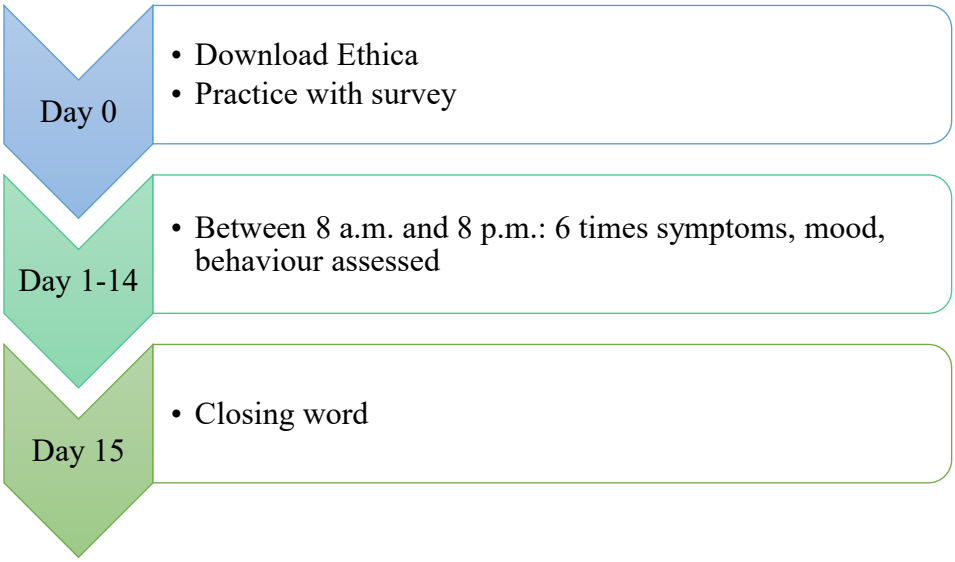
The mean age of the sample was 59.7 years (*SD* = 7.65), ranging from 48 to 76 years. The gender was equally distributed, with five female (*n*=5, 50%) and five male (*n*=5, 50%) participants. The BMI was, on average, 31.7, indicating obesity in the sample. More specifically, 40% of the sample was overweight (*n* = 4), 20% had a healthy weight (*n* = 2), and 40% were obese (*n*=4). The educational level varied within the sample. 30% of the sample had at least the education level of junior general secondary education (MAVO) (*n*=3), 20% had higher vocational education (*n*=2), and the last 20% were differently educated from lower vocational education (LTS) (*n*=1) to university (WO) (*n*=1). The majority of the sample (*n*=8, 80%) indicated having one or more comorbidities like heart and vascular diseases, high blood pressure, lung disease, diabetes etc.

Design

This experience sampling study is based on previous studies and the guidelines of Conner and Lehman (2012). As suggested by an analysis of ESM on mobile devices by Van Berkel et al. (2017), the study lasted for 14 days; see Figure 2 for a visual representation. The study used a signal-contingent sampling strategy, meaning the participants received unpredictable notifications within two-hour intervals (Conner & Lehman, 2012). Optimal test results are predicted with an amount of five to eight measures per day which is why this study measured their participants six times per day (Klasnja et al., 2008).

Figure 2

Flowchart of the Study Design



Materials

The daily assessment consisted of two kinds of surveys, one retrospective sleep survey in the morning once a day and a momentary symptom, mood, and behavior survey six times a day. In total, 16 variables were measured in the ESM study based on multiple validated relevant questionnaires (Brys et al., 2020; Dietvorst et al., 2021; Jean et al., 2020; Lenaert et al., 2020; Maes et al., 2015; Worm-Smeitink et al., 2021). For the current paper, brain fog and depressed mood were of importance. Next to that, demographic characteristics were also measured, like gender, age, body mass index (BMI) and comorbidities.

Brain Fog

Brain fog was measured with one item by Kratz et al. (2017), indicating the ability to think on a numerical rating scale from 0 to 10 (see Appendix A). The item was 'how is your 'thinking' at the moment (original: hoe gaat het met uw 'denken' op dit moment?). Zero indicates 'thinking is hard and slow' (original: het denken gaat moeilijk en langzaam) and 10 indicates 'thinking is fast; I am alert and sharp' (original: het denken gaat snel; ik ben alert en scherp).

Depressed Mood

Depressed mood was measured with one item based on the Hamilton Rating Scale for Depression (HRSD-NL), namely 'I feel depressed right now' (original: Op dit moment voel ik mij somber) (see Appendix A). The participants were able to rate on a 7-point Likert scale ranging from one (strongly disagree or original: sterk mee oneens) to seven (strongly agree or original: sterk mee eens). The item is in line with items from previous ESM studies (Brys et al., 2020; Worm-Smeitink et al., 2021).

Procedure

The study was approved by the Ethics Committee of the Faculty of Behavioral, Management and Social Sciences of the University of Twente (request number: 210799) and the Medisch Spectrum Twente Institutional Review Board (request K20-30). Data was gathered between September 1 and November 5, 2021. The ESM study was conducted using the platform Ethica Data (Ethica Data, 2022) on the participants' smartphones. The research team conducted a pilot test on a student with post-COVID symptoms to fix practical issues in the Ethica questionnaires. Before the interview, the participants had already signed informed consent and agreed after the interview to join the ESM study. At the official start of the current study, participants needed to download Ethica and sign another informed consent by Ethica. The mood and symptom surveys were sent out each day at six unpredictable points of

time within equal two-hour intervals for 14 consecutive days. After 15 minutes, the surveys expired, and notifications disappeared to reduce the burden on the participants and avoid memory biases. With the first survey in the morning, sleep quality was additionally assessed.

Data Analysis

The statistical program SPSS version 28 (International Business Corporation) was used to analyze the ESM data. Based on the guideline of Cohen (1988), when standardized β was >.1 (-.1), it was considered a small effect, >.3 (-.3) was considered a moderate effect, and >.5 (-.5) was considered a strong effect. Statistical outcomes were considered significant at a two-sided alpha level of .05 or lower. Since this study was part of a more extensive study, only variables of interest were investigated, namely brain fog and depressed mood.

Firstly, descriptive statistics were performed, and visualizations were created to achieve an overall impression of the sample and variables of interest. Next, the variable brain fog was created by recoding the outcome of the question from ten being the highest indication of being able to concentrate to zero brain fog, nine to a one, etc., so that finally zero indicated no brain fog and 10 indicated high brain fog. To account for the multilevel structure of the data and the multiple observations nested within participants, linear mixed models (LMM) were used to answer all RQs. Since the study took place for 14 consecutive days, the chance of missing one or more assessments was high, which LMMs can deal with. They are able to handle large amounts of missing data and data that is not independent (clustered or nested) (Verhagen et al., 2016). Due to the assumption that correlations between measurements exponentially decline and have homogenous variances, a First-order Autoregressive (AR(1)) covariance type was selected (Kincaid, 2005). In all LMMs, participants were set as subjects and measurement timepoints as repeated measurements. To estimate the strength of associations, all relevant variables were transformed into z-scores. The analyses were then conducted with standardized scores.

For the first RQ concerning the experience of brain fog and depressed mood over time, two LMMs were conducted to obtain descriptive statistics. The estimated mean scores of depressive mood and brain fog were then represented on average and for each individual, respectively, on graphs, summed over the total assessment period of 14 days of the study. Moreover, the estimated mean scores of depressed mood and brain fog were represented on average and for each individual on graphs, depicting the course of the variables over the day.

To answer the second RQ concerning the momentary association of brain fog and depressed mood, another LMM was performed. Here, brain fog was the dependent variable, and depressed mood was the fixed covariate.

For the third RQ, the between-person association and within-person association needed to be tested. Therefore, the person mean score for the between-person association and the person-mean centered score for the within-person association of depressed mood were computed using the Aggregate function in SPSS (Curran & Bauer, 2011). An LMM was performed with brain fog set as the dependent variable, and the person-mean centered score and person mean score of depressed mood were set as fixed covariates.

To answer RQ four and five, one-moment lagged scores (T-1) (Alliger & Williams, 1993) of brain fog and depression were computed to see if they predict each other approximately two hours later on the same day. For that, two more LMMs were conducted, one with brain fog as the dependent variable and the lagged variable of depressed mood as the fixed covariate, and one with depressed mood as the dependent variable and lagged brain fog as the fixed covariate to check possible bi-directionality. To reduce the risk of one symptom (brain fog or depressed mood) at T6 (evening day one) predicting the other symptom (depressed mood or brain fog) at T1(morning day two), the first timepoint of each day was filtered out in the analysis.

Results

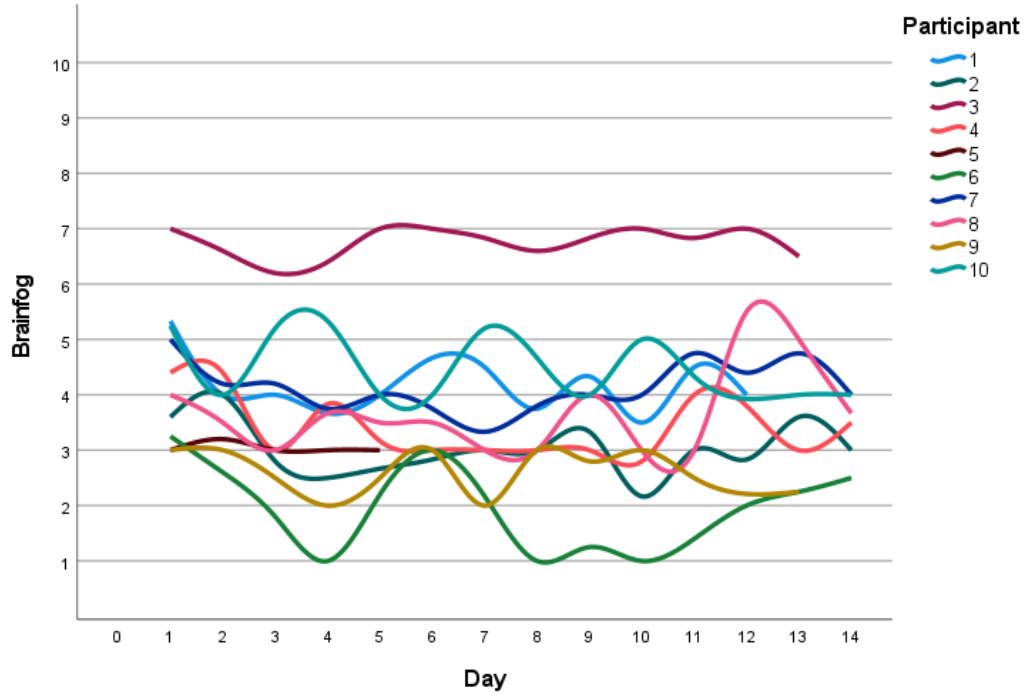
The sample's response rate of variables of interest ranged between 30% to 90%, with a mean response of 61,6% in all measurements (*SD* = 20%). During the total assessment period, the estimated mean brain fog score of the total sample was 3.8 (*SE* = .17), with a range of scores between zero to ten. The estimated mean score of depressed mood of the total sample during the total assessment period was 3.0 (*SE* = .35), with a range of scores between one to seven.

Description of Brain Fog

Figure 3 shows the estimated mean daily brain fog score per person during the total assessment period. Here, strong fluctuations can be noted without any noticeable pattern. The majority fluctuated between a brain fog score of two to six, while two participants (Participants 6 and 3) showed major differences. Participant 6 experienced little brain fog, still with strong fluctuations during the total assessment period. Participant 3, on the other hand, experienced rather strong brain fog with fewer fluctuations.

Figure 3

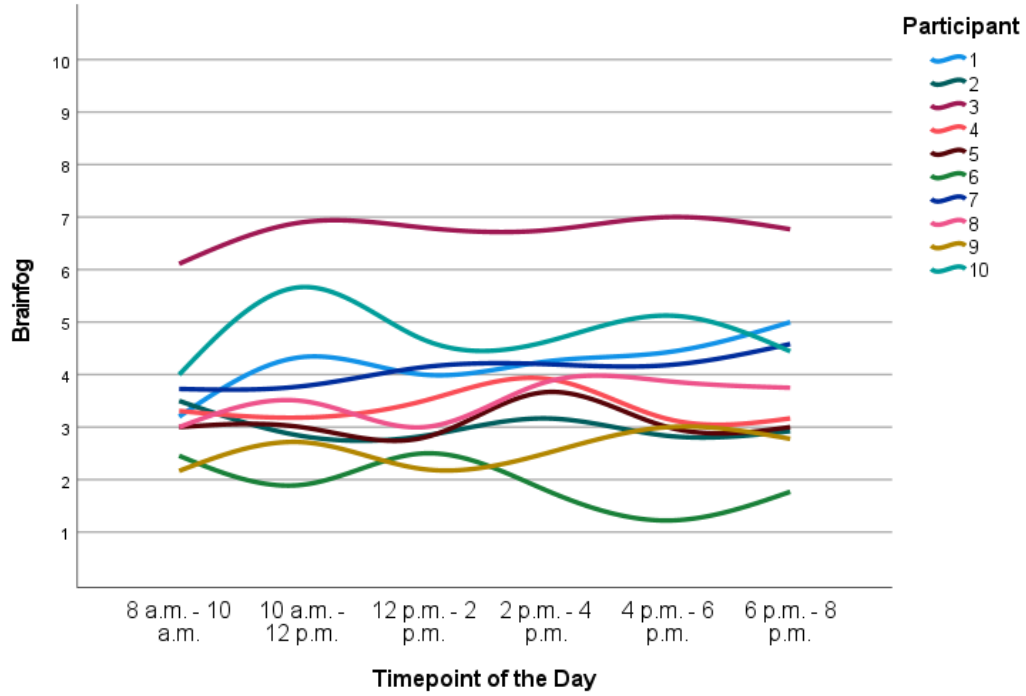
Estimated Mean Daily Brain Fog Score per Person During the Total Assessment Period



When looking at Figure 4, which represents the estimated mean brain fog score per person per timepoint during the day, one can see that the majority of participants tended to have a lower score of brain fog in the morning than in the evening. Still, there was no steady increase during the day but fluctuations without a noticeable pattern. Again, Participants 3 and 6 show differences from the average. Participant 6 experienced brain fog overall a bit lower than the other participants, being the strongest in the morning and the weakest in the afternoon between 4 and 6 p.m. Participant 3 experienced brain fog stronger than the average, with the lowest score in the morning, an increase until between 10 a.m. and 12 p.m. and then relatively stable scores during the day.

Figure 4

Estimated Mean Brain Fog Score per Person per Timepoint of the Day During the Total Assessment Period



Description of Depressed Mood

When looking at Figure 5 representing the estimated mean daily depressed mood score per person during the total assessment period, one can see that there was no clear pattern in the experience of depressed mood among the single participants. The majority fluctuated between a depressed mood score of two to five. Some experienced higher depressed mood on all days (Participant 3 and Participant 7), while others experienced almost no depressed mood at all (Participants 10, 9 and 2). The individual fluctuations were also very distinctive from each other.

Figure 5

Estimated Mean Daily Depressed Mood Score per Person During the Total Assessment Period

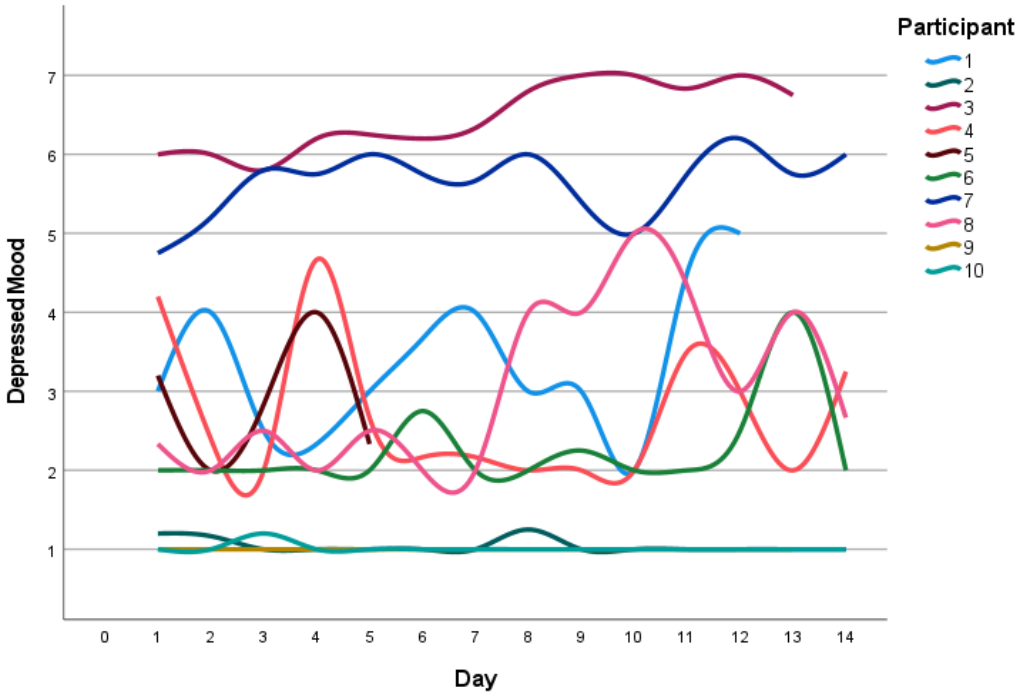
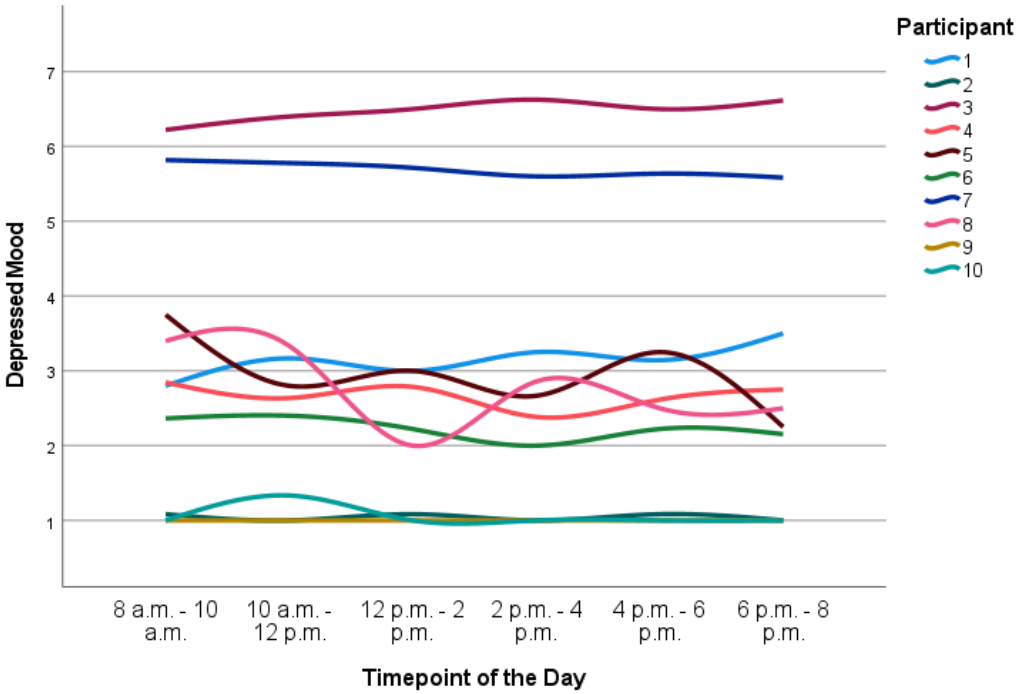


Figure 6 shows the estimated mean depressed mood score per person per timepoint during the day. Here, no clear pattern can be noticed; some participants experienced more depressed mood in the morning, and for some, it increased more towards the evening. Also, here some participants experienced higher depressed mood over the day (e.g., Participant 3 and Participant 7) while others experienced not much depressed mood (Participants 10, 9 and 2).

Figure 6

Estimated Mean Depressed Mood Score per Person per Timepoint During the Day for the Total Assessment Period



Description of Depressed Mood and Brain Fog

Looking at Figure 7, one can see the display of the groups' estimated mean depressed mood and brain fog together at all timepoints. One can see similar fluctuations of the two symptoms over all assessment timepoints. Most of the time, the fluctuations were stronger in one of the symptoms, but the timepoint and direction of the fluctuation were often the same.

Two participants were noticeable in their strength and fluctuation of depressed mood and brain fog. Firstly, Figure 8 shows the course of depressed mood and brain fog together at all timepoints for Participant 3. Both scores were relatively high, with many fluctuations. Next, Figure 9 shows the course of depressed mood and brain fog together at all timepoints for Participant 2. Here, one can see that both scores were relatively low, with only little fluctuations in depressed mood and many in brain fog. Graphs displaying the course of depressed mood and brain fog of all participants can be found in Appendix B.

Figure 7

Line Plot Depicting Standardized Scores of Mean Depressed Mood and Mean Brain Fog for all Assessment Points of All Participants

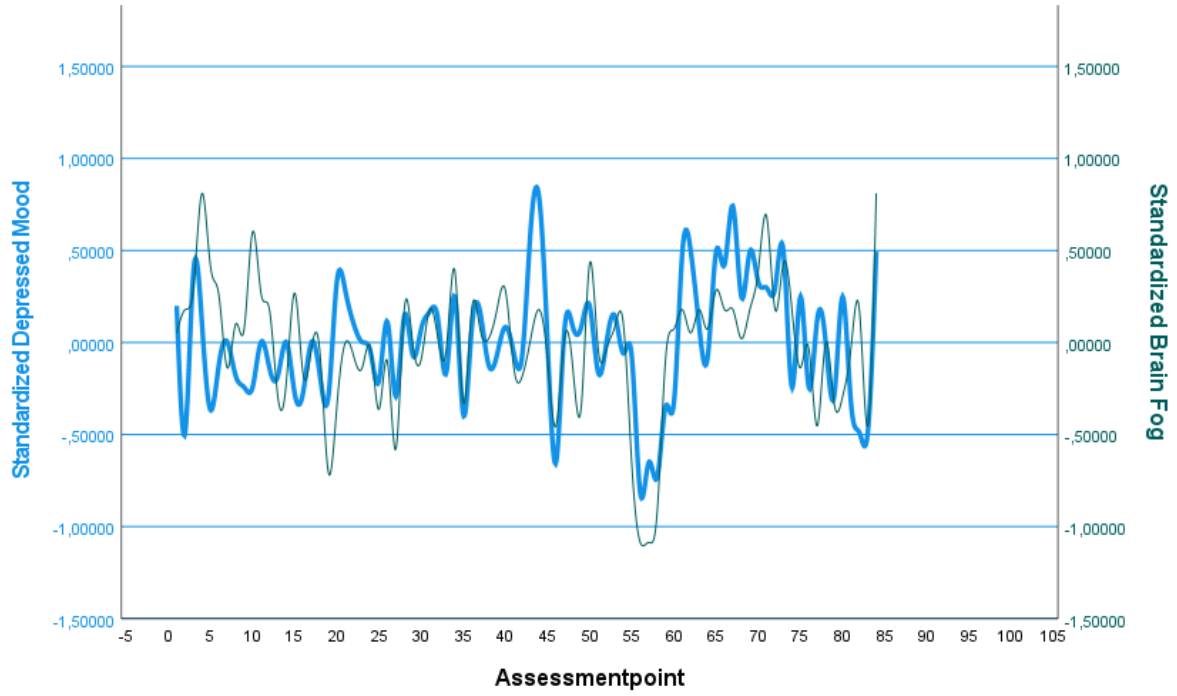


Figure 8

Line Plot Depicting Standardized Depressed Mood and Standardized Brain Fog Scores per Assessment Point for Participant 3

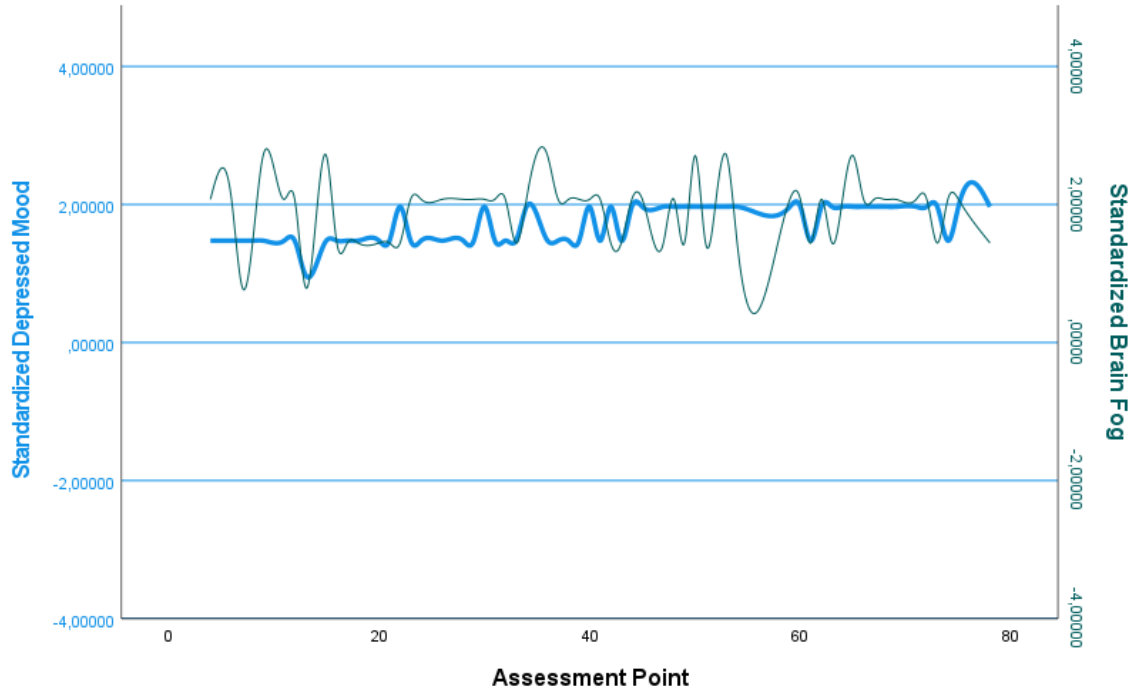
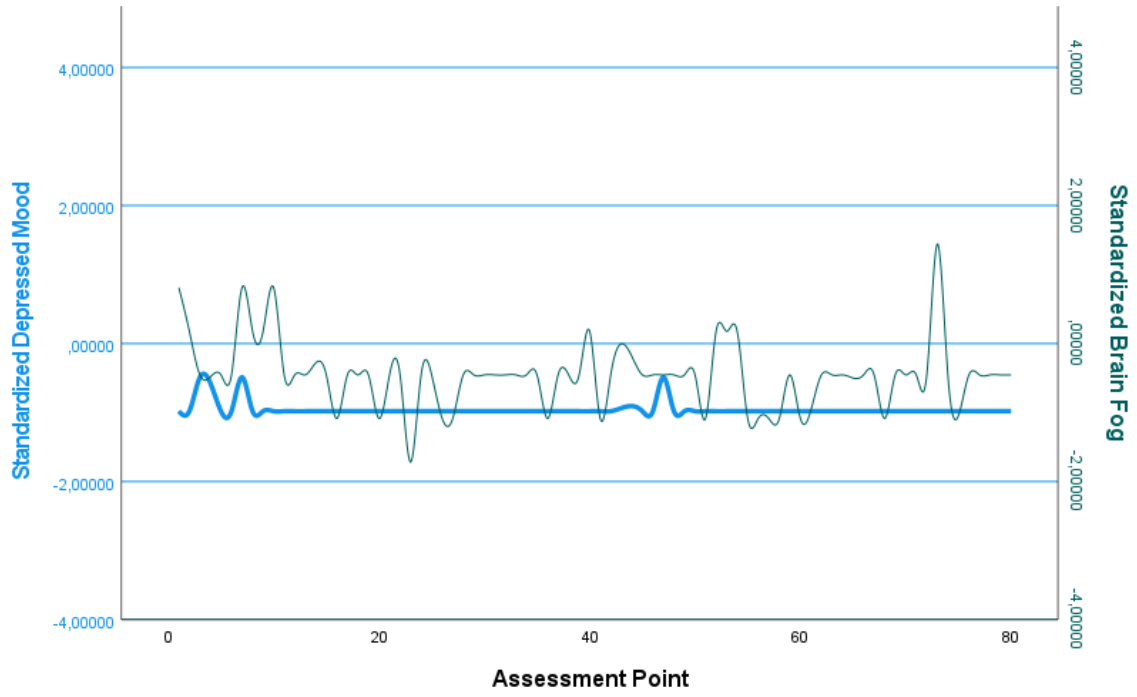


Figure 9

Line Plot Depicting Standardized Depressed Mood and Standardized Brain Fog Scores per Assessment Point for Participant 2



Momentary Association of Brain Fog and Depressed Mood

The first LMM with brain fog as the dependent variable and depressed mood as the independent variable showed significant results (Table 1). The results revealed a positive, moderate momentary association between these two variables (β=.45; p <.001).

Table 1

Summary of Linear Mixed Model for the Momentary Association Over Time Between Standardized Brain Fog and Depressed Mood

							CI 95%	
Dependent variable	Predictor	β	SE	df	t	p	Lower Bound	Upper Bound
Brain Fog	Depressed Mood	.45	.06	207.94	7.93	<.001	.34	.56

Note. β = Standardized Parameter Estimate, SE = Standard Error, df = Degrees of Freedom, CI = Confidence Intervals

Within- and Between Associations of Brain Fog and Depressed Mood

The between-person association between brain fog and depressed mood was shown to be strong and significant (β =.56; p <.001) (Table 2). Participants with, on average higher (or lower) depressed mood scores than others had strongly higher (or lower) brain fog scores than others. The within-person association was small and significant (β=.11; p <.001). When an individual had higher (or lower) depressed mood scores than their own average, this was only weakly associated with a higher (or lower) brain fog score at that time point. The association between depressed mood and brain fog was mainly a between-person association and much less a within-person association.

Table 2

Summary of Linear Mixed Models for Within- and Between Analysis of Standardized Brain Fog and Depressed Mood

							CI 95%	
Dependent variable	Predictor	β	SE	df	t	p	Lower Bound	Upper Bound
Brain Fog	Depressed Mood (PM)	.56	.07	55.59	7.80	<.001	.42	.71
	Depressed Mood (PMC)	.11	.03	452.96	3.95	<.001	.05	.16

Note. β = Standardized Parameter Estimate, SE = Standard Error, df = Degrees of Freedom, CI = Confidence Intervals, PM = Person-mean, PMC = Person-mean centered

Predictive Associations between Brain Fog and Depressed Mood

When analyzing if depressed mood (lagged variable) predicted brain fog at the next measurement (approximately two hours later on the same day), no significant outcome was found. To check if brain fog predicts depressed mood at the next measurement, another LMM was conducted with lagged brain fog as predictor of depressed mood. The results were also not significant. In sum, the results revealed that depressed mood did not predict brain fog approximately two hours later, nor did brain fog predict depressed mood at the next measurement. More detailed findings of the models are summarized in Table 3.

Table 3

Summary of the Linear Mixed Models for the Analysis of Lagged Standardized Brain Fog and Standardized Depressed Mood

							CI 95%	
Dependent variable	Predictor	*β*	SE	df	t	*p*	Lower Bound	Upper Bound
Brain Fog	Lagged Depressed Mood	.12	.08	126.94	1.44	0.15	-.045	.283
Depressed Mood	Lagged Brain Fog	-.003	.04	280.96	-.09	.93	-.08	.07

Note. *β* = Standardized Parameter Estimate, SE = Standard Error, df = Degrees of Freedom, CI = Confidence Intervals, Lagged = Variable at the next measurement

Discussion

The current longitudinal ESM study was, to our knowledge, the first study aiming to examine the course of and interplay between brain fog and depressed mood in patients with post-covid symptoms, including differentiating the experience of the variables on a state-like level and trait-like level. Furthermore, it was tested if there was any predicting relationship over time between the two variables.

Descriptive results showed that the sample experienced, on average, moderate and continuous brain fog and felt moderately and continuously depressed. Strong fluctuations were found in brain fog during the total assessment period, but no noticeable pattern. During the day, the sample experienced, on average, a bit less brain fog in the morning than in the evening, here with minor fluctuations and no steady increase. Regarding depressed mood, the results showed that the sample experienced strong fluctuations during the total assessment period with no noticeable pattern. During the day, the experience of depressed mood is for some individuals strongly fluctuated, for some only a little, but altogether it does not follow a diurnal pattern either. Considering all results, no clear pattern was found for the experience of brain fog or depressed mood. The individual experience of the symptoms is very distinctive from each other in fluctuations and strength. Furthermore, a momentary moderate and positive association between depressed mood and brain fog could be found. Meaning if the sample experienced higher (or lower) depressed mood, they were also likely to experience higher (or lower) brain fog at the same moment. This association was found to be mainly on a trait-like level, more than on an state-like level, meaning participants with, on average more (or less) depressed mood than others also experienced more (or less) brain fog than others. In contrast, when an individual had more (or less) depressed mood compared to their own average, they were only a bit more likely to experience more (or less) brain fog at that time point. When exploring this association further, it was found that even though depressed mood and brain fog are associated, they do not predict each other over time. More specifically, if somebody experienced depressed mood, they were not likely to experience brain fog approximately two hours later, nor was depressed mood predicted by brain fog approximately two hours later.

In line with previous research among populations with post-COVID, depressed mood and brain fog were also experienced in this sample (Brown & O'Brien, 2021; Reinfeld, 2022). Depressed mood was experienced as fluctuating over the assessment period of 14 days, which is in line with findings from Mehlan (2021), who also found that depressed mood fluctuates over time. Still, against expectations due to findings from Rossi and Rossi (1977), no pattern

according to the weekdays and weekends could be found. However, they conducted research among young adults, while the sample of this study had a higher age. The experience of depressed mood of the single participants was very individually. Brain fog was also experienced differently among the individual participants over the assessment period of 14 days, with no noticeable pattern regarding the week's structure and many fluctuations. Depressed mood and brain fog increased and decreased on average only little over the day. While some individuals experienced brain fog most strongly in the morning, the majority of the sample experienced brain fog a bit lower in the morning than in the evening. This is against expectations compared to the findings of Ross et al. (2013), who found that people with postural tachycardia syndrome experience brain fog the strongest in the morning. This could indicate that brain fog among people with post-COVID is experienced differently or has different causes than in people with postural tachycardia syndrome, although more research would be necessary to confirm. Depressed mood was experienced very differently amongst the individual participants during the day with no noticeable pattern, which is in line with previous results. In an experience sampling study with cancer patients, no clear diurnal pattern was either found in mood over the day (Schouten, 2021). Concluding, the RQ '*How are brain fog and depressed mood subjectively experienced over time in Dutch people with post-COVID six months after hospital discharge?*' can be answered by having, on average continuous and moderate levels of both brain fog and depressed mood, which fluctuate over the day and during the assessment period. Still, the experience differs a lot among the single participants in intensity as well as in course over the day and the total assessment period of 14 days. Some experienced the symptoms very strongly while others barely at all. Nevertheless, the findings show that depressed mood and brain fog are common health hazards among people with post-COVID, supporting previous findings (Krishnan et al., 2022; Kamal et al., 2021). Both symptoms should be taken seriously and treated appropriately to minimize the suffering of patients with post-COVID. Since Saltzman et al. (2020) found an association between poor mental health and social isolation due to hospitalization, especially patients who were hospitalized, like in this sample, should be supported more after their discharge to improve their potentially decreased mental health. This also applies to the treatment of brain fog since Asadi-Pooya et al. (2022) saw the risk of brain fog increased after more severe courses of COVID-19, which is usually the reason for hospitalization.

Furthermore, in line with expectations, a momentary moderate and positive association between brain fog and depressed mood could be found. This is in line with previous studies investigating the association between brain fog and depressed mood among post-COVID

patients (Cristillo et al., 2022). This association could be explained by experiencing a hyperawareness of cognition when showing depressive symptoms (Orfei et al., 2022). Meaning the subjective experience of brain fog might be generated, perpetuated or exacerbated by depressive symptoms, such as depressed mood. Another explanation could be that depressed mood influences the activity of certain brain regions implicated in cognitive functions, as Mayberg et al. (1999) found. Depressed mood in both healthy and clinically depressed participants influenced the activity of prefrontal and limbic brain regions. Many of these regions are also involved in cognitive functions, which could explain why brain fog and depressed mood were associated. In line with these suggestions, the article of Parker (2022) states that while brain fog is a depression sub-typing symptom, it is fascinating to see that only those individuals who depict themselves as having depressed mood experience brain fog. In contrast, those individuals who suffer from clinical depression but do not experience depressed mood do also not experience brain fog. Overall, based on the results of this study, the second RQ, *'Is there an association between depressed mood and brain fog in Dutch people with post-COVID six months after hospital discharge?*', can be answered with yes, there was a momentary association between depressed mood and brain fog in Dutch people with post-COVID six months after hospital discharge. This information can be used to improve the treatment among post-COVID patients since one could treat both symptoms simultaneously and increase the well-being of patients. Since depressed mood belongs to the spectrum of symptoms of major depressive episodes, treatment options could consist of cognitive behavioral therapy or counselling (Davey, 2021). There is also the possibility of taking antidepressant drugs, depending on the severity of depressed mood. On the other hand, treating brain fog should primarily focus on optimizing exercise, sleep and reducing stress (Krishnan et al., 2022). Altogether, a joint treatment of both symptoms might lead to increased health.

To answer the third RQ, the association between depressed mood and brain fog was examined further by distinguishing between the two levels of the association. It was found that the association is mainly a trait-like (between-person) association more than a state-like (within-person) association. This means that someone who experienced generally more (or less) depressed mood than another person would also experience more (or less) brain fog than another person. On the other hand, when individuals experienced more (or less) depressed mood than they usually did, they were only a bit more likely to experience more (or less) brain fog than usual. These findings cannot be directly compared to other studies in post-COVID patients, nor with other studies concerning brain fog and depressed mood, since the

distinction between between-person and within-person associations in depressed mood and brain fog has to our knowledge, not been studied yet. However, studies investigated the association between depressed mood and brain fog on a trait-like level. Orfei et al. (2022) found that depressive and other mood disorder symptoms are associated with brain fog in the general population. This is in line with the findings of Cristillo et al. (2022), who found a significant correlation between self-rated depressive symptoms and brain fog. Taking the results of this study into regard, the third RQ, '*What is the between-person and within-person association between brain fog and depressed mood in Dutch people with post-COVID six months after hospital discharge?'*, can be answered with even though the associations are significant on both levels, the association between depressed mood and brain fog is different in comparison and acts mainly on a trait-like level and only little on state-like level. Therefore, according to the results of this study, when experiencing (more or less) depressed mood, this person is more likely to experience (more or less) brain fog in than another person. On the other hand, when an individual experiences (more or less) depressed mood than they usually do, they are only a little bit more likely to experience (more or less) brain fog than they usually do. When applying that knowledge, one could focus on treating patients with post-COVID who experience more depressed mood than others also on treating brain fog, since according to this study, they are more susceptible to experiencing brain fog than others.

When exploring the association between depressed mood and brain fog further, it was checked if the variables predict each other over time, as Cristillo et al. (2022) implied a possible prediction of cognitive complaints by depressive symptoms. This study´s results revealed that experiencing increased (or decreased) depressed mood did not predict increased (or decreased) brain fog approximately two hours later in people with post-COVID. The results also showed that changes in brain fog did not predict changes in depressed mood at the next measurement in people with post-COVID. Therefore, RQ four, '*Does depressed mood predict brain fog over time in Dutch people with post-COVID six months after hospital discharge?'* can be answered by no, depressed mood does not predict brain fog over time in Dutch people with post-COVID six months after hospital discharge. RQ five, '*Does brain fog predict depressed mood over time in Dutch people with post-COVID six months after hospital discharge?'* also has to be answered with no, against expectations due to suggestions of Miskowiak et al. (2021) who implied an increased depressed mood because of increased cognitive impairments. In this study, brain fog does not predict depressed mood over time in Dutch people with post-COVID six months after hospital. Nevertheless, it is possible that other underlying mechanisms may cause both depressed mood and brain fog since they are

still momentarily associated. Hereby, the high percentage of comorbidities and obesity in the sample should be noted, which may play a role in inducing depressed mood and brain fog. Also, other underlying mutual factors in the relationship between depressive mood and brain fog are possible. For this, more research needs to be conducted.

Strengths and Limitations

A major strength of the study was using ESM for the first time to explore depressed mood and brain fog in people with post-COVID over time. By using ESM, rich information about the experience and relationship between the variables over 14 days could be obtained. The association between depressed mood and brain fog has not been thoroughly researched yet, especially not within post-COVID patients, since this is a relatively new field of research. In contrast to cross-sectional studies, participants of the current study reported their momentary symptoms and experiences during the assessment period. With that, memory biases could be avoided due to multiple measurements during the day and short time distances between the event and the assessment (Conner & Lehman, 2012). Furthermore, the association of depressed mood and brain fog between persons and within individuals was studied, which gives more detailed insight into the kind of association between the two variables and how depressed mood relates to brain fog on a trait-like level, as well as on a state-like level (Myin-Germeys & Kuppens, 2021). Another strength of this study was that the variables of interest were not only examined for momentary associations but also for prediction over time. By performing the analysis with lagged variables, potential directional influences could be checked.

A limitation of the current study was that the variables of interest were assessed with single-item questions. As depressed mood and brain fog are multifaceted symptoms, this limits the insight into the exact state of the participants. It also limits the generalizability to other populations since there was no information about the psychometrics of the items of the current study.

Another limitation of this study is the relatively small sample size. Even though ESM is not dependent on big sample sizes to maximize validity and reliability (Verhagen et al., 2016), it would offer richer data. Additionally, the sample was obese, had multiple comorbidities, only one nationality (Dutch), a quite limited range of age (48 to 76 years, with a mean of 59.7 years) and was hospitalized in the same hospital, which may limit the generalizability of the current study's findings. A larger sample with more variability in nationality, age, location of hospital and other characteristics could increase the generalizability.

Future Research

Based on the limitations of this study, a bigger sample with more variability in various characteristics should be chosen in future research to see if the results would be replicated in a sample with different demographics. Age variability seems especially relevant since the course of COVID-19 was shown to be more severe among older people (Lithander et al., 2020). Next, the sample should also include post-COVID patients with no comorbidity since this sample's comorbidity rate was relatively high (80%), which has been shown to influence the COVID-19 symptoms (Malik, 2022; Lithander et al., 2020). In sum, a larger sample with more diverse characteristics would be a suitable approach for future research.

Another approach for future studies would be to include more items or ask open questions to offer the participants more possibilities to express their exact experience concerning depressed mood and brain fog, e.g., which aspects of thinking are impacted at the moment or asking more detailed what makes the participants' mood depressed. As Mazza et al. (2022) stated, there are many reasons patients with post-COVID experience depressed mood, like uncertainty about the future, social isolation, vast exposure to media, or survivor guilt. Still, in the frame of the current study, this could have led to less compliance since the overall study investigated multiple constructs besides depressed mood and brain fog. Additionally, items with information about psychometrics should be included to allow comparison with other populations.

One last approach for future research would be to examine depressed mood and brain fog in shorter periods of time and check for a prediction effect again. Since the measurement points in this study were always around two hours apart, it is hard to say if one symptom predicts the other over such an extended period. Additionally, a prolonged assessment period in total would offer richer insight into the experience of depressed mood and brain fog since this study was conducted for only 14 days. Also, a different kind of analysis, such as a cross-lagged panel analysis with structural equation modelling to study relationships in both directions over time between variables simultaneously, would be more suiting for analyzing possible causal relationships (Kenny, 1975). Hereby, taking possible underlying factors into consideration would be important to gather more insight into the interplay between depressive mood and brain fog.

Conclusion

In conclusion, the current ESM study was the first study to collect longitudinal data about depressed mood and brain fog in post-COVID patients after hospital discharge. Depressed mood and brain fog were found to be continuous and moderate symptoms with

fluctuations during the day and over the total assessment period, although the experience differed among the individuals. There was a positive, moderate association between depressed mood and brain fog, whereas this association acted mainly on a trait-like level and less on a state-like level. This means people with (more or less) depressed mood were more likely to experience (more or less) brain fog than others, but the individual was only a bit more likely to experience (more or less) brain fog when experiencing (more or less) depressed mood than they usually did. This distinction between the two symptoms was not researched before. The level of depressed mood did not predict an increased or decreased level of brain fog approximately two hours later. Since the research field around post-COVID is relatively new, this study contributes to research and potentially enhancing treatment options among post-COVID patients.

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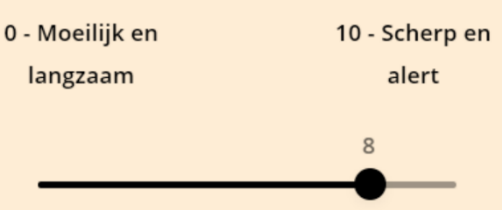
Appendices

Appendix A: Symptoms and Complaints Surveys.

Only variables of interest will be shown.

Komt 6x per dag, tussen 08.00 en 20.00. Blijft 15 minuten lang open zonder herinnering. / *Comes 6x per day between 08.00 o´clock and 20.00 o´clock. Accessible for 15 minutes without reminder.*

9. Hoe gaat het met uw '**denken**' (concentratie, geheugen, aandacht) op dit moment? '0' betekent dat het denken langzaam en moeilijk gaat '10' betekent dat het denken scherp en alert is. Klik op onderstaande lijn om te beginnen. / *How is your **'thinking'** (concentration, memory, attention) right now? '0' means that your thinking goes slow and hard, '10' means that your thinking is sharp and alert. Click the line below to start.*



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

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

Appendix B: Line Plots Depressed Mood and Brain Fog per Participant

Figure B1

Line Plot Depicting Standardized Depressed Mood and Standardized Brain Fog Scores per Assessment Point for Participant 1

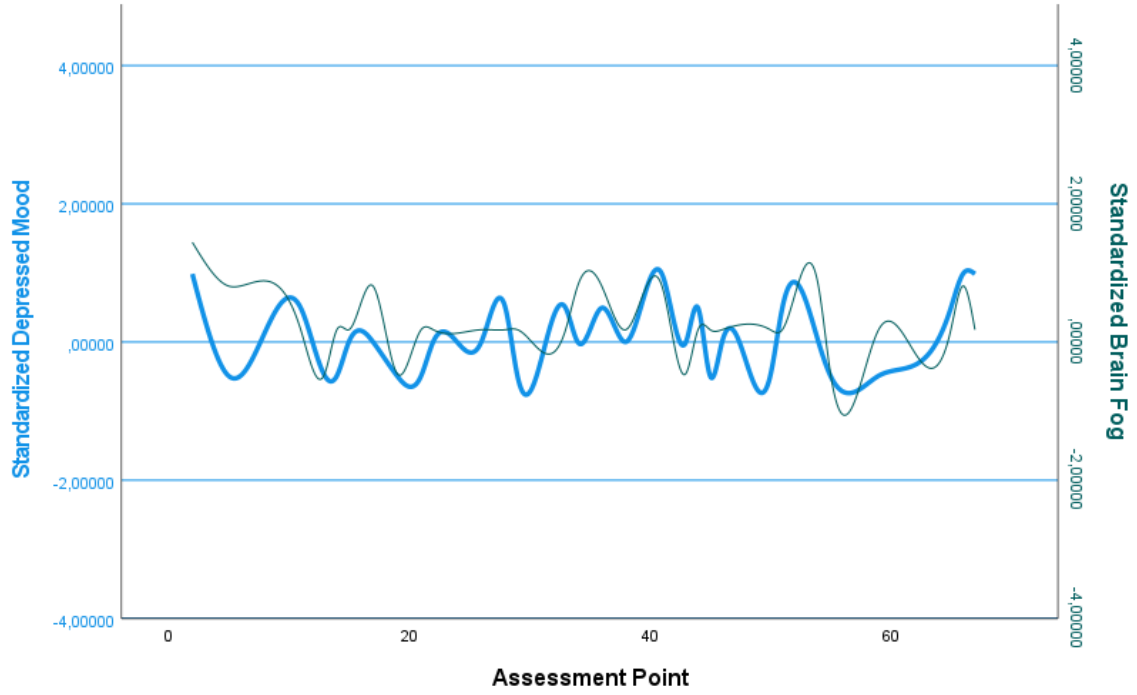


Figure B2

Line Plot Depicting Standardized Depressed Mood and Standardized Brain Fog Scores per Assessment Point for Participant 2

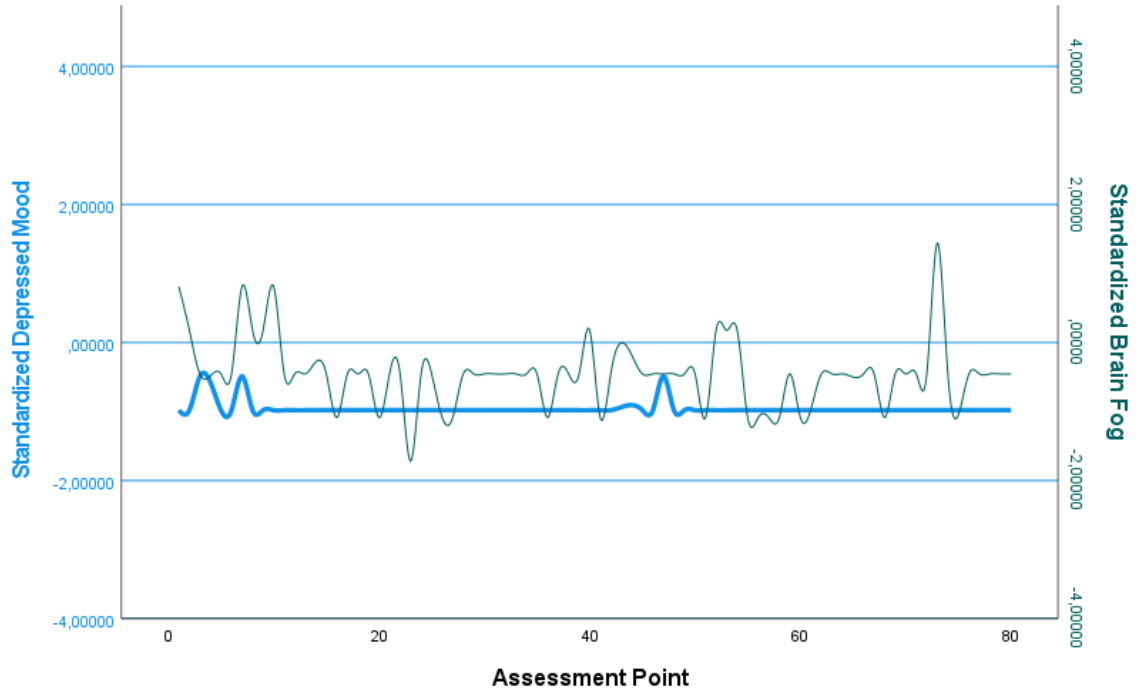


Figure B3

Line Plot Depicting Standardized Depressed Mood and Standardized Brain Fog Scores per Assessment Point for Participant 3

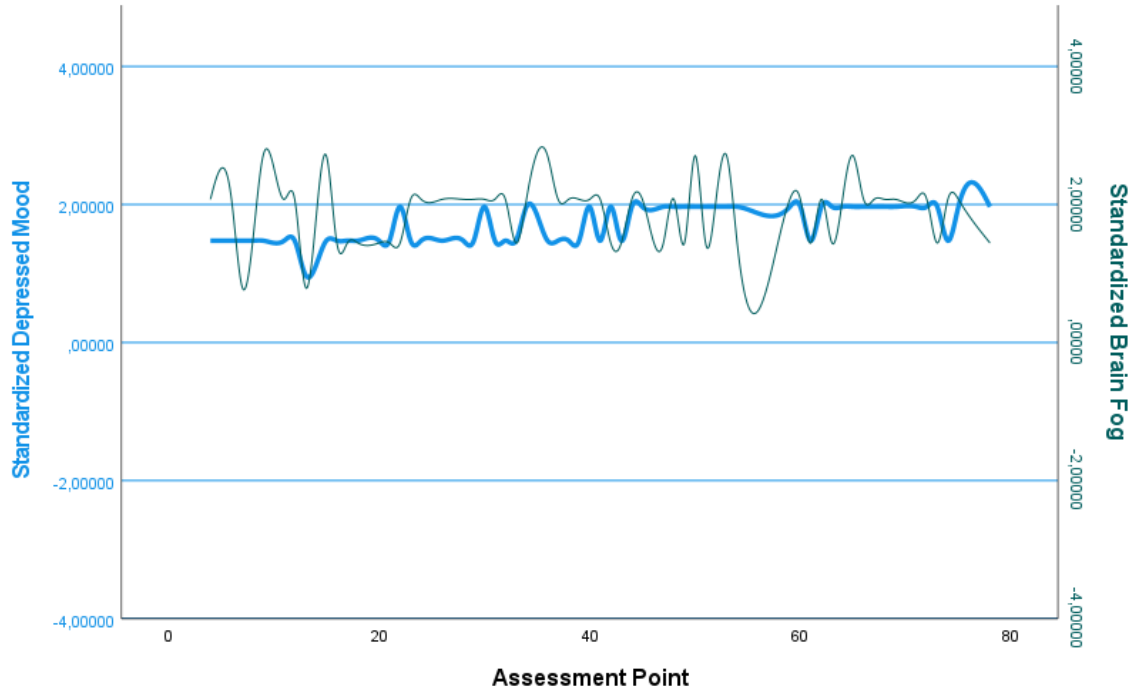


Figure B4

Line Plot Depicting Standardized Depressed Mood and Standardized Brain Fog Scores per Assessment Point for Participant 4

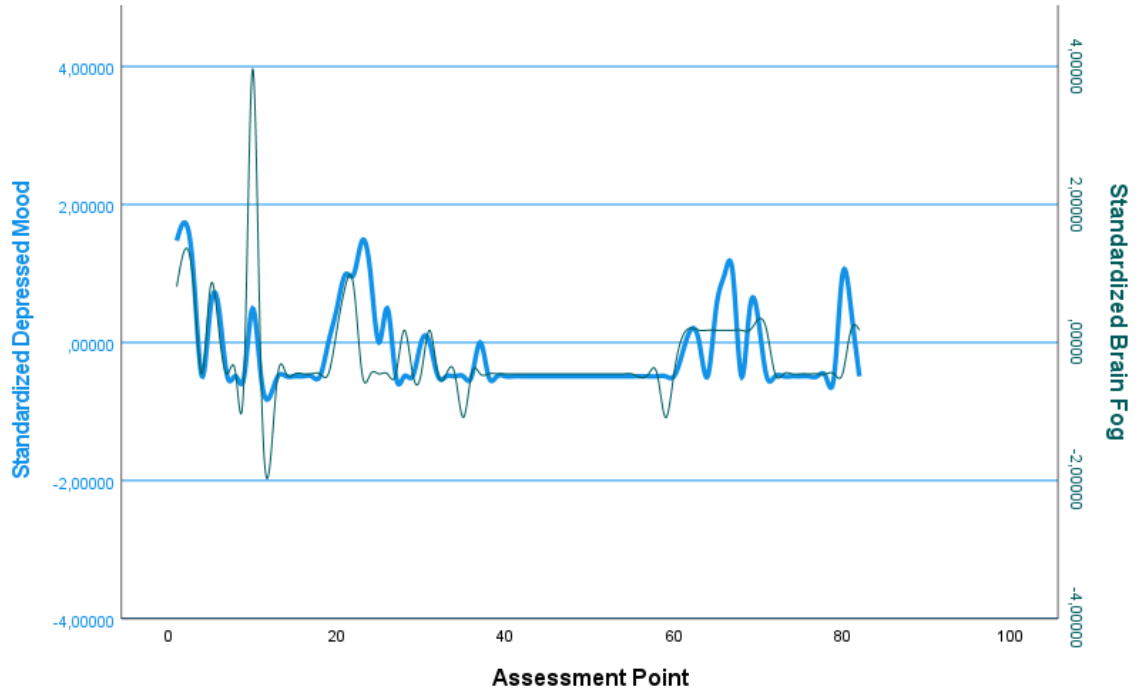


Figure B5

Line Plot Depicting Standardized Depressed Mood and Standardized Brain Fog Scores per Assessment Point for Participant 5

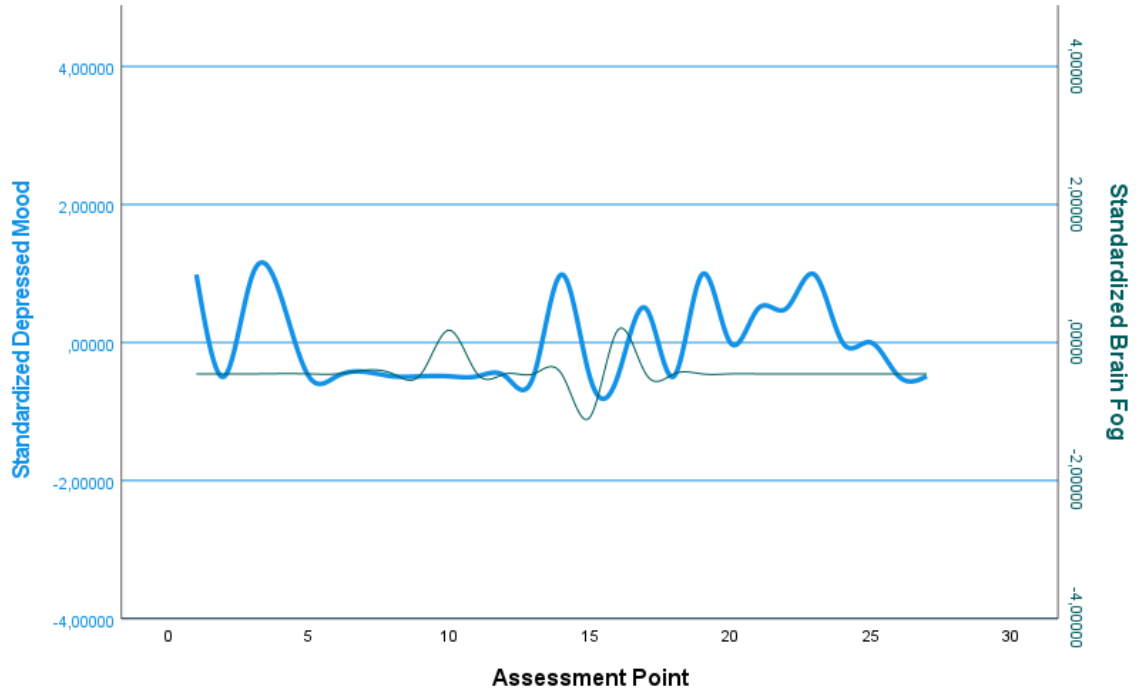


Figure B6

Line Plot Depicting Standardized Depressed Mood and Standardized Brain Fog Scores per Assessment Point for Participant 6

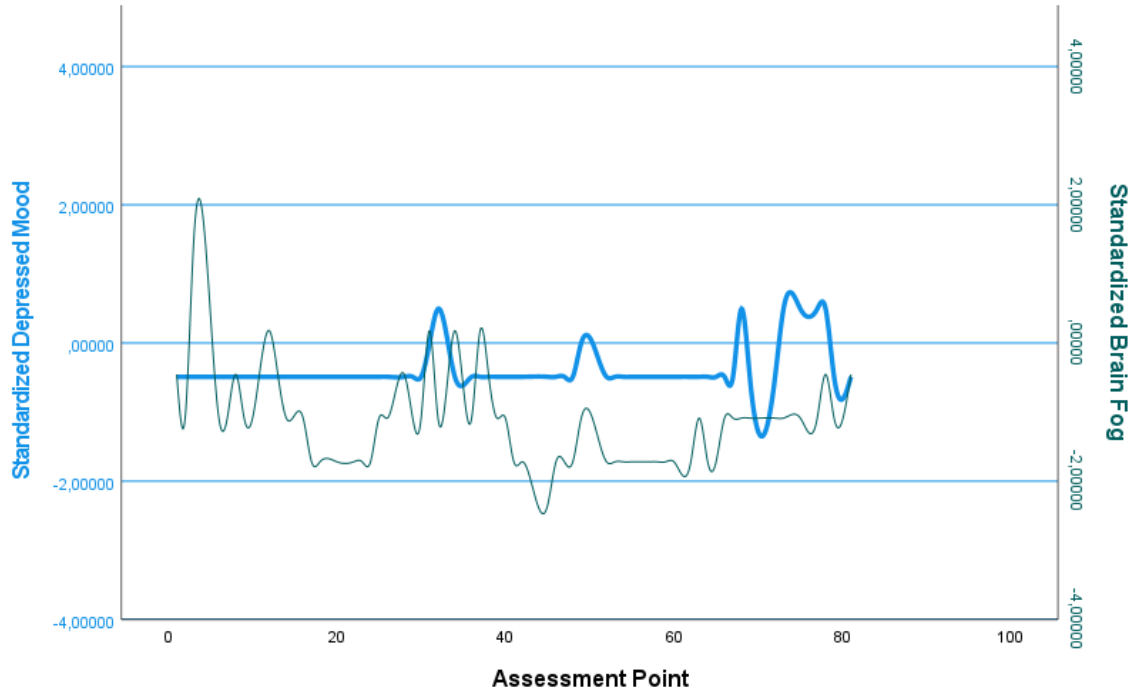


Figure B7

Line Plot Depicting Standardized Depressed Mood and Standardized Brain Fog Scores per Assessment Point for Participant 7

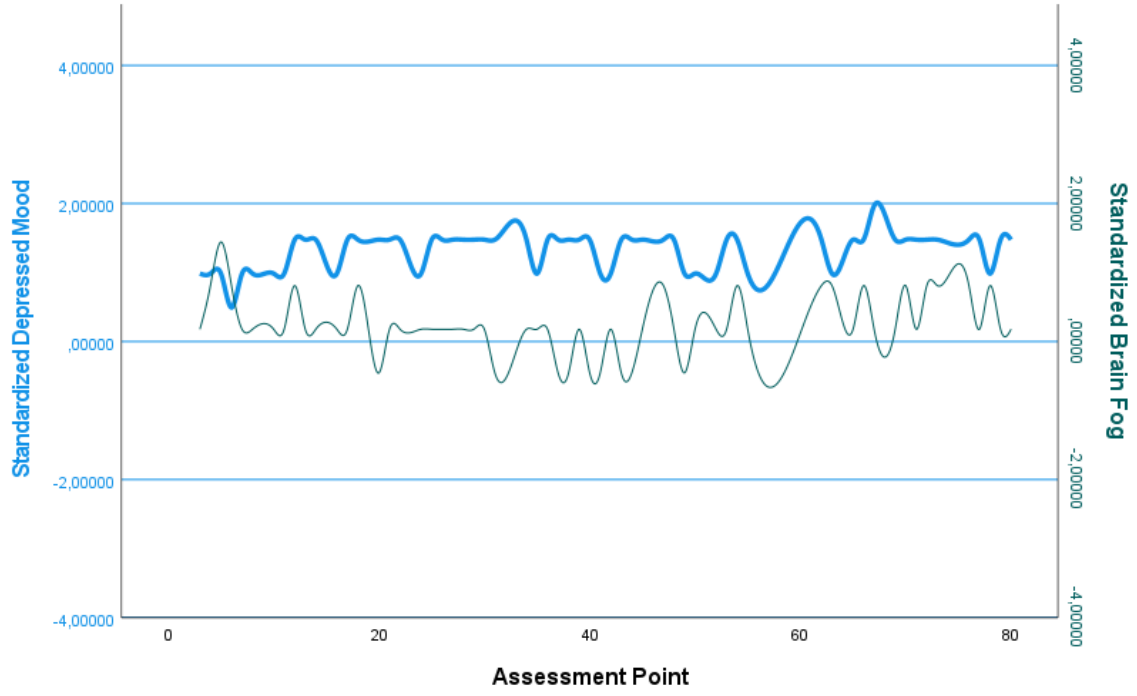


Figure B8

Line Plot Depicting Standardized Depressed Mood and Standardized Brain Fog Scores per Assessment Point for Participant 8

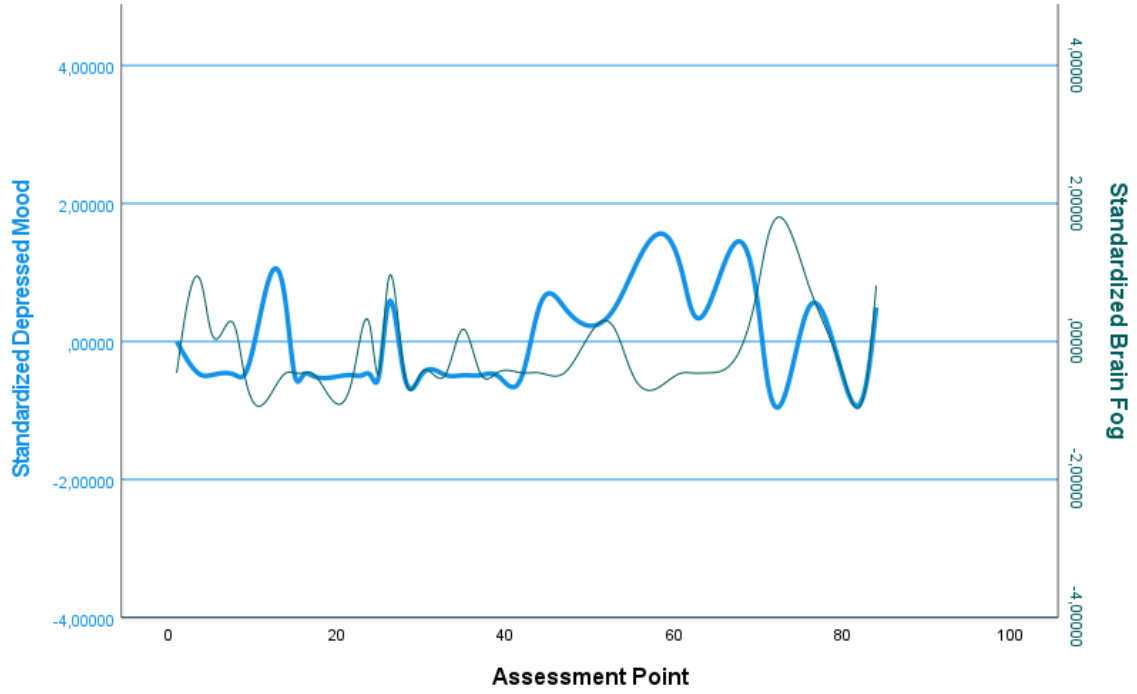


Figure B9

Line Plot Depicting Standardized Depressed Mood and Standardized Brain Fog Scores per Assessment Point for Participant 9

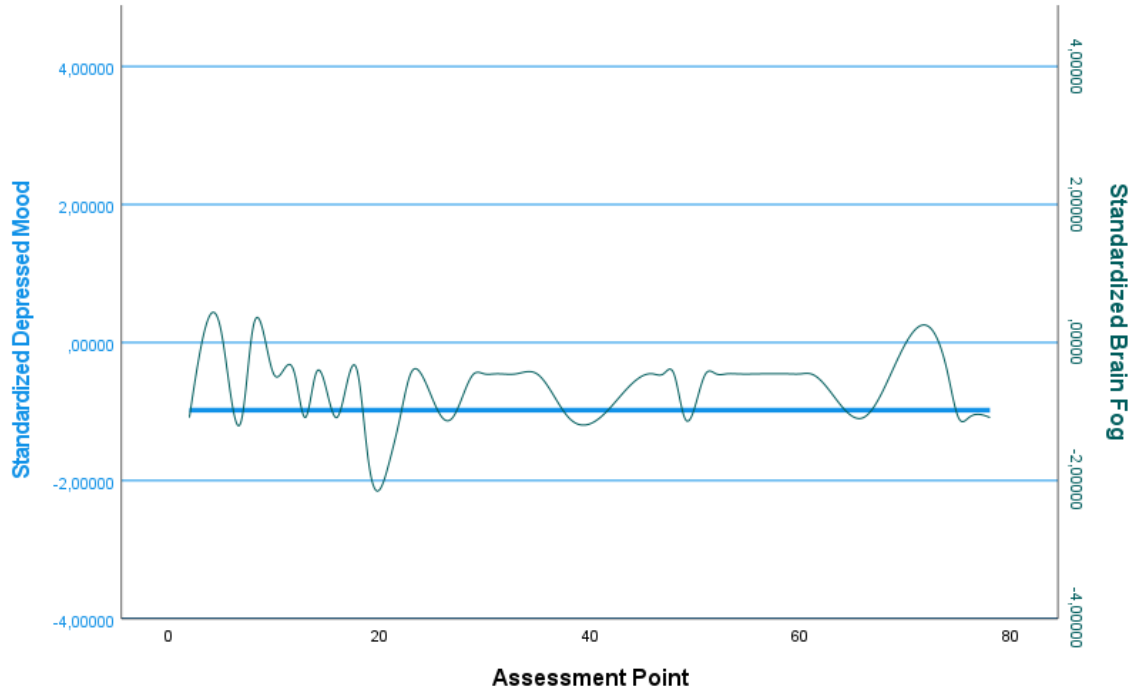


Figure B10

Line Plot Depicting Standardized Depressed Mood and Standardized Brain Fog Scores per Assessment Point for Participant 10