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A Closer Look at Post COVID-19 Subjective Fatigue and its relationship with Quality of Life in a Dutch and German Sample

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Abstract

Objective: Fatigue is one of the most common symptoms experienced during previous and current COVID-19 pandemic(s). After delineating a definition of subjective fatigue that applies to the self-report instrument used in the Cognition & COVID-19 study (COCO-19) which is "a subjective lack of mental and/or physical energy that is clearly interfering with normal functioning according to the self and others (Calabresi & Pitteri, 2018) in addition to subjective fatigue defined as a debilitating feeling of both physical and mental tiredness or exhaustion, characterized by lack of energy, concentration and initiative, slowed reactions, sleepiness and finally, muscle weakness (Ortelli, 2021), the present research aims to explore the subjectiveness of fatigue symptoms collected via self-report, analyze their relation to COVID-19 severity and contribution to Quality of Life.

Methods: Participants were asked to fill out the COCO-19 test battery (Cognition & COVID-19), a sequence of questionnaires belonging to four domains: neuropsychology, psychology, quality of life and personality. The responses of the two main samples of infected participants (n=147) and healthy controls (n=73) of subjective fatigue as measured by the Fatigue Severity Scale were analyzed in three different ways. To compare the means of the two samples a two-tailed independent sample t-test was used. To measure whether severity of subjective fatigue reflected an increase of severity of experienced illness, a one-way ANOVA and post-hoc analysis was performed. Finally, a multiple regression analysis was performed to explore the impact of subjective fatigue and other constructs that might influence Quality of Life according to research such as sleep quality as measured by the Pittsburgh Sleep Quality Index (PSQI), Neuroticism measured by the NEO-FFI Neuroticism scale and subjective illness severity.

Results: Subjective fatigue was found to be higher amongst participants who were affected by COVID-19 compared to controls. Even participants who had a milder course of disease were found to experience severe subjective fatigue. Subjective fatigue contributes greatly to Quality of Life indices, followed by subjective sleep quality and finally by the subjective severity of COVID-19 infection, as opposed to neuroticism.

Conclusion: Subjective fatigue shows an increase in incidence in case of COVID-19 diagnosis, and grows in severity whenever participants subjectively experience more severe COVID-19 symptoms. Furthermore, subjective fatigue shows a great influence on Quality of Life. Practical implications of these findings are discussed in the final sections of this thesis.

Keywords: subjective fatigue, COVID-19, Quality of Life

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State of Science

Towards the end of 2019 a novel virus by the name of *severe acute respiratory syndrome coronavirus 2*, or SARS-CoV-2, of the class of the corona viruses began its infectious course in Wuhan, China. Early in the following year, the spread was classified as a pandemic by the World Health Organization (WHO). As the infection rates rose the symptomatic nature characterizing the virus unfolded. Being a coronavirus, like SARS and MERS, this virus shares the seemingly non-lethal diagnosis of a flu that mainly affects the respiratory tracts (Borges do Nascimento, 2020). In fact, the virus infiltrates host cells by binding its spike protein to our angiotensin converting enzyme 2 (ACE-2) (Ou X, 2020), present in great numbers in the lungs (Imai, 2010).

The virus has been shown to affect more than just the lungs however. Gastrointestinal symptoms (Wang et al. 2020), heart complications (Zheng, 2020) and multi organ failure (Vos, 2020) are some examples of the many consequences the virus brings. In addition to these symptoms, a striking percentage of the infected population experiences a more subtle but nevertheless long-lasting symptom; fatigue (Ortelli, 2021).

Incidence of fatigue during pandemics

Fatigue has been a common denominator in the scientific literature regarding the coronaviruses and other viral infections as one of the most common symptomatic manifestations both in the acute and chronic state (Islam, 2020). For example, fatigue was observed post SARS by Tansey et al. in Canada (2007) and by Lam et al in Hong Kong (2009) in longitudinal studies. Both research groups concluded that the majority of their sample experienced fatigue through

recovery chronically. Similarly during other pandemics, fatigue has been explored by Magnus et al. (2015) post Influenza A (N1H1) in Norway and in a sample of Ebola virus survivors by Wilson et al. in 2018.

Similarly, fatigue was recorded frequently during the present pandemic as well. For instance, fatigue seems to persist chronically post COVID-19 infection in an Italian sample (Carfì & Landi, 2020), as well as being one of the most prevalent symptoms according to Davis et al. (2020). Del Rio (2020), Goerts (2020) and Lads (2020) agree on the persistence of fatigue in the period ranging from three to six months after COVID-19 diagnosis, being one of the most prevalent and debilitating symptoms experienced by their samples in the United States, the Netherlands and United Kingdom respectively. Mandal et al. (2021) argues that fatigue persists in 69% of the population affected by COVID-19. Together with other symptoms such as non-restorative sleep and depressive symptoms this cluster of symptoms will eventually evolve into a "Post-COVID-19 Syndrome" (Perrin, 2020). Developing such a clinical profile would threaten the already endangered health care system, as more and more people would seek help to ameliorate their symptoms (Perrin, 2020). The assumption is that fatigue-like symptoms are a concerning manifestation in the post-infection phase and that they need to be tackled in order to lower the probability of a vast decline in Quality of Life in the affected population during this pandemic.

Characterization of Fatigue

Despite the high incidence, fatigue still lacks a clear definition in the clinical setting (DeLuca, 2005). That is due to its multidimensional and elusive nature, as fatigue can manifest

both as a symptom and a disease, can depend on a comorbid chronic illness (Johansson, 2008) and can be measured both subjectively and objectively (De Luca, 2005). For example, on the one hand, fatigue as a disease can be recognized as a so-called "unexplained" illness like Chronic Fatigue Syndrome (CFS), which presents a disabling and pervasive feeling of fatigue that impairs global functioning for a substantial period of time by unknown cause (Niloofar, 2003). On the other hand, fatigue can be assessed as a mere symptom, manifesting comorbidly with (amongst many others) sleep deprivation (Morris & Miller, 1996), Traumatic Brain Injury (TBI) (Riese, 1999), cancer (Wagner, 2004) and numerous psychiatric disorders (Harvey, 2009).

The abundant nuances of this construct result in the lack of a universal consensus on its explicit definition (DeLuca J., 2005). However, one way to help the characterization of subjective fatigue comes from its difference with fatigue that is measured with objective testing (de Luca, 2005). In fact, objective fatigue reflects cognitive dysfunction (Mosso, 1904. Wessley, 1998), such as a decline in working memory, short term memory (Johnson, 1997) or executive functioning (Krupp & Elkins, 2000). On the contrary, subjective fatigue does not contribute to objectively measured cognitive decline but shows interference with activities of daily living (Calabresi & Pitteri, 2018). Once this distinction is made, it could be inferred that self-reported fatigue deserves to be explored within the context of infections as much as objectively measured fatigue, as it is of great interest to explore the general well-being of people in their daily lives during the pandemic.

The literature seems to converge on the subjective characterization of fatigue, as self-reported fatigue can be observed as a subjective lack of mental and/or physical energy that is clearly interfering with normal functioning according to the self and others (Calabresi & Pitteri, 2018). To further explain, subjective fatigue can be defined as a debilitating feeling of both

physical and mental tiredness or exhaustion, characterized by lack of energy, concentration and initiative, slowed reactions, sleepiness and finally, muscle weakness (Ortelli, 2021). For instance, persistent feeling of fatigue in TBI patients can result in a decline in social and occupational functioning even long after other post-injury symptoms have resolved (Stulemeijer, 2006).

It has to be noted that fatigue often manifests prominently in concomitance with other conditions, complicating the act of studying it by itself. To name a few, Dai et al. (2020) suggests the comorbidity between fatigue and Cardiovascular Disease (CVD) in his Henan sample. Furthermore, there seems to be a co-occurrence between fatigue and depression (Calabresi & Pitteri, 2018). Sleep deprivation is another factor that is commonly assessed as a causal factor (Strober, 2015). Wessely (2000) proposes a quite outstanding overlap between several psychiatric disorders and fatigue. Furthermore, Yamada (2003) explores a correlation between the state of being anxious and generalized anxiety with fatigue. Finally, regarding personality traits and tendencies, neuroticism seems to be a strong predictor of exaggerated complaints about subjective health status that is usually unrelated to the actual health status (Natelson, 1996).

Nonetheless, fatigue can be explored when taking into account its separate mechanisms in medical conditions, possibly excluding the causal relationship between fatigue and other co-occurring factors (Leavitt, 2010). For example, in the case of CVD, fatigue contributes the most to future cardiac events as opposed to depression (Siegel, 2005), thus, separating the two factors as independent mechanisms. Furthermore, fatigue and sleepiness diverge in their neural apparatus, as sleep has a strong biological base whilst fatigue only vaguely involves it (Duntley, 2005).

Relationship between Fatigue and Quality of Life

Subjective fatigue and the study of its consequences on other aspects of daily living is indeed to be prioritized during this pandemic. Reason is that it has been observed in the past that fatigue is a symptom that appears more often than not, in cases of poor Quality of Life, which usually strikes the population during pandemics (Ahmed, 2020). Poor Quality of life is an extremely concerning component for the well-being of people, as it sparks a vast collection of health and social (Amdal, 2021), and employment issues (Auriel, 2009). Moreover, extensive poor Quality of Life greatly aggravates the healthcare system, health providers and general practitioners (Malik, 2021).

Newer research in the context of the current pandemic explores the great number of people experiencing a decline in Quality of Life after COVID-19 diagnosis. Interestingly, the evaluation of the degree of Quality of Life decline reflects observations investigated in the past pandemics of SARS and MERS after infections as seen in the meta-analysis by Salawu et al. (2020). Results show that lower Quality of Life was observed as long as one year after initial assessment. Furthermore, impaired Quality of Life persevered two years after Influenza A diagnosis (Chen, 2017). During the SARS-CoV-2 pandemic, an overall lower Quality of Life was reported up to three (Tavahomi, 2021) and six months after infection (Townsend, 2021). Finally, Malik conducted a meta-analysis exposing a pool prevalence of poor Quality of Life after COVID-19 diagnosis of 59% (2021).

Poor Quality of Life seems to persist long-term COVID-19 infection (Townsend, 2021), and impacts several daily living aspects, such as the ability to return to work (Townsend, 2021) or the participation in social activities (Amdal et al., 2021). Townsend suggests that long-lasting

issues with Quality of Life manifest irrespectively to initial severity of COVID-19 diagnosis (2021). It could be in fact, that Quality of Life declines regardless of magnitude of infection and instead results from other, more psychologically related, additive effects such as sleep disturbances or subjective fatigue, as affirmed by Huang (2021).

It has been shown that self-reported fatigue appears to be a major component of poor Quality of Life in a sample of patients with Multiple Sclerosis (MS) observed by Merkelbach (2002). Likewise, Janardhan & Bakshi found a strong correlation between fatigue and Quality of Life in a sample of patients affected by (MS)(2002). Similar results were reproduced in samples of patients affected by ALS (Lou, 2003), haemodialysis (Georgios et al., 2015), cancer (Cella, 1998), Parkinson's Disease (Havlikova, 2008) and coronary heart disease (Staniute, 2014). It has also been suggested that both mental and physical facets of Quality of Life are influenced by fatigue (Benedict, 2005).

Analogous results have been reproduced in the current pandemic. For instance, Amato et al. reports fatigue as one of the independent factors that help to predict Quality of Life in an Italian sample (2020). Similarly, fatigue was found to persistently influence Quality of Life and participation in social activities months after COVID-19 diagnosis (Tabacof, 2022). Malik (2021) additionally found poor Quality of Life to be significantly higher in participants who experienced fatigue compared to the absence of fatigue.

The aforementioned information assists to justify academic interest in the relationship between subjective fatigue and Quality of Life. On top of that, adding supportive data to the ongoing trend will surely contribute to the push for deliverance of more adequate healthcare related interventions and rehabilitation for long-term effects of COVID-19 infection. In fact, in

accordance with Bryson (2020) amongst other authors, it is necessary to look into factors that might reduce Quality of Life, to prevent them from lingering in society chronically.

Present Study

Fatigue seems to manifest regardless of the magnitude of COVID-19 infection (Maxwell, 2020) in a great number of the affected population. However, it has been argued that the more severe the infection the more probable it is to manifest fatigue by Dai et al. (2020). This study suggests that fatigue is a sign that characterizes a severe COVID-19 infection. However, very little research has been done regarding the association between the severity of the viral infection and the severity of the consequent fatigue.

A prevalent scarcity of subjective measures of fatigue was encountered while collecting research. The scientific community prefers objective measures of fatigue as it is believed they are a more reliable source of data, given the ambiguity of subjective measures (Leavitt, 2010). For instance, Ortelli et al. (2021) used screenings of fatiguing pinching tasks. Even so, there is a growing number of researchers conducting projects using self-reports, such as the Chalder Fatigue Score (Kedor, 2021) or the Multidimensional Fatigue Inventory (Mantovani, 2021). Many others have collected their data electronically (e.g. Carfì & Landi, 2020; Ladds, 2020) without using specific fatigue instruments. This indicates that the current line of research tends to operate according to subjective fatigue scales.

This study has three research aims. First, to explore the subjectiveness of fatigue in the context of COVID-19. Second, the need to fill the gap of knowledge regarding severity of

subjective fatigue and severity of COVID-19 infection. Third, to explore the influence that certain variables present in the COCO-19 test battery have on overall Quality of Life.

For once, the three hypotheses are coherent with a great amount of current research regarding fatigue post-viral infection and fatigue's influence on Quality of Life. Also, the possibility of establishing a novel association between the severity of COVID-19 infection and severity of subjective fatigue is yet to materialize, making this new research a probable significant contributor to current scientific knowledge. At last, it also seems worthwhile to explore the possibility of weighting the influence of different psychological variables included in the COCO-19 on Quality of Life and determine their contribution to it. This thesis could offer cumulative data to the current knowledge regarding the link between fatigue and Quality of Life after COVID-19 infection.

Based on this knowledge, the three hypotheses are as follows:

- H1: It is argued that individuals who were diagnosed with COVID-19 subjectively report fatigue to a greater extent compared to healthy controls.
- H2: Among the individuals affected by COVID-19, more severe COVID-19 symptoms are positively associated with higher levels of subjective self-reports of fatigue compared to the participants experiencing a lesser course of infection.
- H3: Subjective fatigue helps to explain the variance of Quality of Life indices.

Methods

Sampling and Participants

Using an online sampling method, it was possible to recruit a total of 326 participants. The sample consisted of 67 males and 259 females. Furthermore, within this sample, 194 participants declared having had COVID-19 whereas the remaining 132 participants fell into the category of healthy control group, never having had COVID-19.

The Ethics Committee of the Department of Psychology at the University of Groningen has approved this research project. Informed consent was obtained from all participants of the study, before the questionnaire was presented. Participants who did not give their consent or who did not enter a response, were excluded from the analyses. Participants were not (financially or otherwise) compensated for their participation in the current study.

Cognition & COVID-19 Test Battery (COCO-19)

The COCO-19 test battery is a long assessment (>60 minutes) of self-report questionnaires belonging to four domains: neuropsychological, psychological, quality of life and personality. It was created to study these four domains in the midst of the pandemic and to explore the impact of infections on cognitive abilities.

This online questionnaire could be accessed through a link and/or a QR code. Participants were first asked to specify in which among five languages they were most comfortable completing the survey in (Dutch, German, French, English, Spanish), to then proceed to a brief explanation of the purpose of the COCO-19 research. Next, was the informed consent form, followed by demographics including living circumstances, prescribed medication, pre-existing conditions and

whether the participants received a COVID-19 diagnosis. Answering "yes" to the latter led to more specific questions, such as what symptoms participants were affected by, how severe they were and how much they would interfere with daily living.

Recruitment

Recruitment was achieved using online convenience sampling by posting on social media (Facebook, Instagram, LinkedIn) and by spreading the questionnaires to family and friends. In addition, the questionnaire was distributed via flyers among health professionals in the Netherlands, such as general practitioners and workers in a hospital that could spread word further amongst hospitalized patients. The same methods of distribution were used internationally, more specifically in Germany, Mexico and Spain.

Fatigue Severity Scale Questionnaire

Given the emphasis on subjective measures onto which the COCO-19 research is based, the definition of fatigue given by Ortelli (2021) and Calabresi & Pitteri (2018) will serve for the purpose of this inquiry. The subjective instrument in use in this study is the Fatigue Severity Scale (FSS), which was located in the second half of the test battery, together with other questionnaires of psychological nature.

One additional intent of the present study is to provide a clear and simple characterization of self-reported fatigue according to the questionnaire in use, the Fatigue Severity Scale (FSS) (Table 2). This nine item questionnaire was at first established as valid in Multiple Sclerosis

(MS) and Systematic Lupus Erythematosus (SLE) samples (Krupp, 1989). This questionnaire has been suggested in later years to have robust psychometric properties (Whitehead, 2009) and to be a valid and reliable instrument of data collection in other disorders and pathologies, such as Major Depressive Disorder (MDD) (Friedberg, 1994), stroke (Lerdal, 2009) and Parkinson's Disease (PD) (Abe, 2000). More specifically, the FSS measures the impact of fatigue symptoms on multiple aspects of daily functioning (Ferentinos, 2011), assessing concepts related both to perceived physical and mental energy as presented in Table 2. The FSS seems to be in line with the definition of subjective fatigue given by Ortelli and Calabresi & Pitteri. Thus, it is adequate to consider the FSS as a just instrument to measure subjective fatigue as it is defined in this present study.

Most importantly, it can be argued that using a subjective instrument of fatigue is paramount, as the pandemic has generated an extensive array of reasons to feel fatigued that are not strictly related to any pre-existing conditions and that cannot be traced down to physical or cognitive testing (Morgul, 2021). Fear for health, safety and economic related variables of the self and others challenges the population's tolerance to stress and burden (Morgul, 2021). Similarly, self-isolation, social distancing, diminished physical activity and sedentary behavior related to schooling or jobs (Javad Koohsari, 2021), disturbances in sleep patterns and others, could aggravate subjective fatigue (Morgul, 2021). Indeed, there seems to be an outbreak of subjective fatigue (Javad Koohsari, 2021), which has adverse effects on wellbeing, productivity, Quality of Life and work performance (Taylor, 2019). Moreover, it is quite alarming that the persistent perception of fatigue could indicate the underlying presence of a psychiatric illness, as the duration of fatigue seems to increase the chance of a psychiatric diagnosis (Clare, 1986), not to mention that fatigue is common in several psychiatric disorders as one of the most debilitating

symptoms (Lewis & Wessely, 1992). It seems that subjective fatigue is more closely associated with psychiatric disturbances rather than motor or objective measures of performance (Millikin et al., 2003). It is therefore urgent to explore subjective fatigue in the context of this pandemic as a preventative measure against the possible decline of mental health and general Quality of Life.

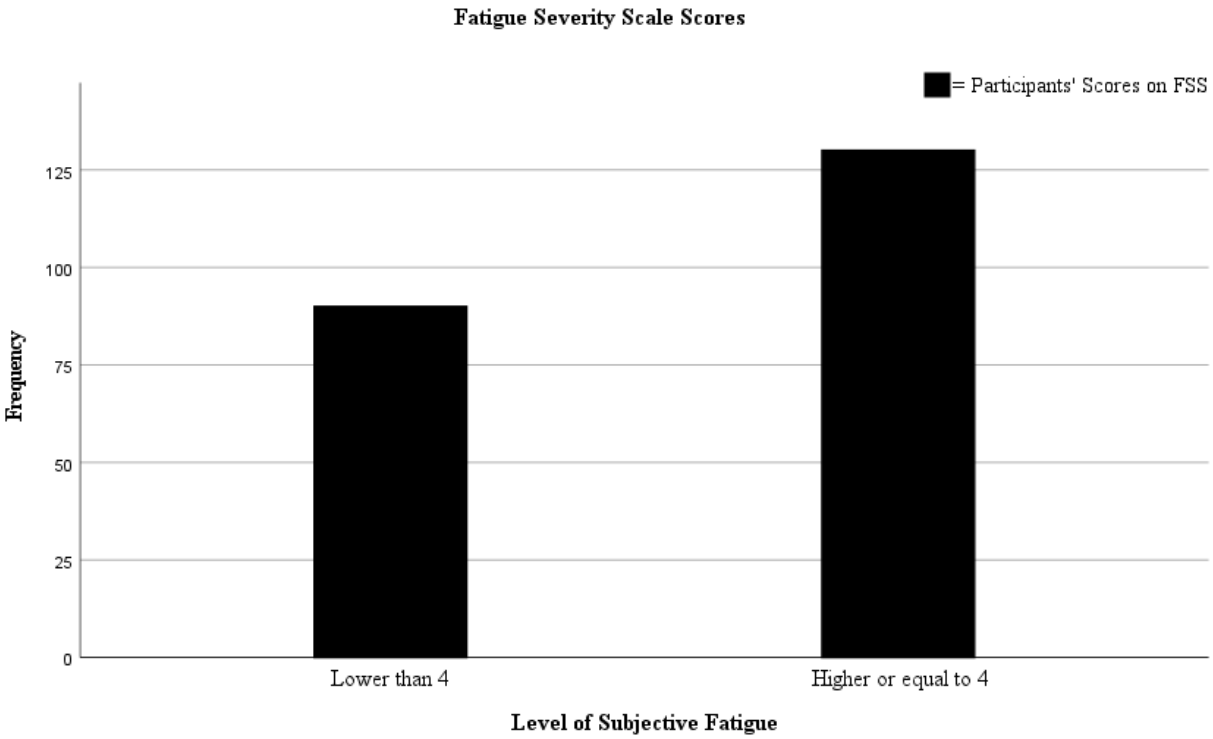
Self-report on Fatigue

The Fatigue Severity Scale (FSS), is a self-report questionnaire meant to quantify the severity of fatigue and its impact on physical functioning, motivation or interference with various aspects of daily living, like work and social activities (Enoka & Duchateau, 2017). The FSS comprises nine items scored on a 7-point likert scale (1=strongly disagree, 7=strongly agree). The minimum score for this test is 9, whereas the maximum score is 63. Once the responses are collected they are numerically averaged across the nine items. A mean score equal or higher than 4.0 indicates a significant level of reported fatigue (Krupp, 1989). Ultimately, 130 (59,1%) participants showed a higher level of reported fatigue compared to the 90 that scored under 4,0 (Figure 3). Out of the 130 participants who scored above 4,0 , 114 (87%) had COVID-19.

It has to be noted that instead of using a 7-point scale, from one to seven, a likert scale from zero to seven was erroneously used in the dutch sample. To dispose of this issue, a simple algorithm was created. Numbers belonging to the dutch data were transformed using this formula; “adj.score = score+ 6/7” apart from every zero, which was transformed into a “1”, and all the “7”, which were kept as “7”. Applying this formula allowed the re-scaling of the Dutch data into numbers fit for the manual rules of the FSS and for statistical analyses.

Figure 1

Fatigue Severity Scale Scores Following Manual Threshold of 4.0



Inclusion & Exclusion criteria

Reason to exclude participants from the statistical analyses was a denied or missing informed consent. Three of such cases were found. Moreover, participants were excluded if their completion time was suspiciously low, meaning they only opened and quickly closed the questionnaire tab without answering any of the questions. In addition, participants who failed to respond to the nine FSS items were excluded, as those responses are paramount for the completion of this thesis. Applying the latter criterion resulted in a good amount of participants being excluded from the analyses (106). That is because the FSS was located towards the end of the questionnaire. Not unreasonably, sustaining the entire length questionnaire (>60 minutes) led

participants to exit the link before answering the FSS and to complete the full COCO-19 test battery. As unfair as it sounds, this matter was taken into account while generating the test battery. In fact, it was not expected of every participant to wholeheartedly follow through the entirety of the COCO-19 questionnaire.

Final sample

Following the application of the exclusion criteria, the ultimate sample consisted of N= 220 participants (n=170 females, n=50 males). Additionally, 147 participants (66,8%) declared being diagnosed with COVID-19 whereas the remaining 73 participants (33,2%) formed the healthy control group, never having had COVID-19. Within this sample, 98 (44,5%) participants were Dutch, and 122 (55,5%) participants were German. In terms of mean age, the largest age groups were ages between 18 and 29, and 50 and 64, where 64 (29,1%) and 71 (32,3%) participants belong to, respectively. Additional demographics included comorbidities, e.g. suffering from a psychological, neurological or psychiatric illness. 29 participants declared having comorbidities of such category and 32 of them specified taking medication for it. Moreover, 18 participants indicated being obese (8,2%), 16 participants suffering from high blood pressure (7,3%) and 7 having diabetes (3,2%). More detailed demographic information is summarized in Table 1.

Table 1
Demographic details of participants

		N	Percentage
Age	18 - 29	64	29.1%
	30 - 39	37	16.8%
	40 - 49	40	18.2%

	50 - 64	71	32.3%
	< 65	8	3.6%
Gender	Female	169	76.8%
	Male	51	23.2%
Marital Status	Married/ In a relationship	107	48.6%
	Widowed	4	1.8%
	Divorced	13	5.9%
	Single	96	43.6%
Education	No degree	1	.5%
	High School Diploma	2	.9%
	Training / apprenticeship	46	20.9%
	Studies without degree	43	19.5%
	Bachelor degree	57	25.9%
	Master degree	31	14.1%
	PhD	34	15.5%
Work Status	Employed (1-39 hours per week)	102	46.4%
	Employed (40+ hours per week)	32	14.5%
	Self-employed	17	7.7%
	Full Time student	33	15.0%
	Housewife/Househusband	4	1.8%
	Unemployed looking for work	2	.9%
	Unemployed not looking for work	4	1.8%
	Retired	14	6.4%
	Not able to work	12	5.5%
Living Situation	House	124	56.4%
	Flat	88	40.0%
	Student House	5	2.3%
	Other (Specify)	3	1.4%
Sport	Never	61	27.7%
	Once a week	52	23.6%
	2-3 times a week	79	35.9%
	Almost everyday	28	12.7%
Movement (per day)	30 minutes or less	67	30.5%
	30 minutes to 2 hours	134	60.9%
	2 to 4 hours	10	4.5%
	More than 4 hours	9	4.1%
Existing Psychological	Yes	29	13.2%
	No	191	86.8%

Illness

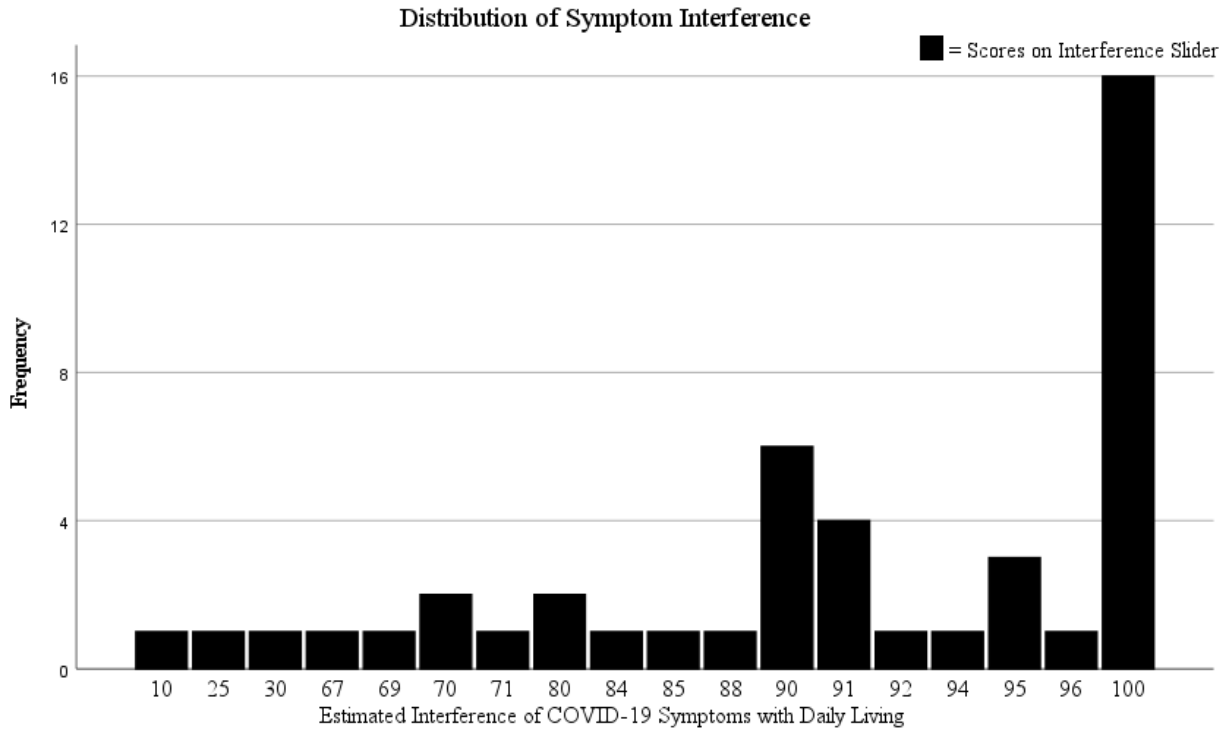
Medication for psychological illness	Yes	32	14.5%
	No	188	85.5%
COVID-19 Diagnosis	Yes	147	66.8%
	No	73	33.2%
Typical Symptoms	Yes	140	95.2%
	No	7	4.8%

Measures of experienced COVID-19 disease severity

Looking at the sample, of the 147 participants who declared having had COVID-19, 140 participants declared having experienced typical symptoms such as fever, body aches and pain. 9 (4,1%) were hospitalized following diagnosis and 66 (30%) reported using medication to alleviate their symptoms. In addition to symptomatology, other two COVID-19 variables were inserted in the questionnaire to apprehend how severely the symptoms impacted daily functioning. First, a slider from 1 to 100 describing how severe the participants were judging their disease course to be was included (‘Please rate the severity of the disease course’). In the full sample, the mean severity of disease course was 55,80. Later in time, a second slider from 1 to 100 was included, for participants to rate how much their symptoms were interfering with their daily activities (Please rate how much your symptoms interfered with your daily activities). Participants rated the interference of their symptom to be 86,67 on average (Figure 2). Given the retroactive insertion, the participants who answered this slider are fewer compared to the first slider. In fact, a large gap between sample sizes can be seen, having only 41 participants responding to this slider.

Figure 2

Distribution of symptoms' interference



Statistical Analysis

To test whether subjectively reported fatigue is higher in case of COVID-19 diagnosis, a two-tailed independent sample t-test will be performed, exploring the mean differences between the experimental group (COVID-19 diagnosis) and the healthy control group (no COVID-19 diagnosis), with respect to the average scores on the FSS questionnaire. Assumptions of normality and homogeneity of variances were assessed before running the test, and were deemed fulfilled looking at Q-Q plots and Levine's F test.

As per the second hypothesis, a one-way ANOVA was used to compare the mean differences of the four COVID-19 severity groups (healthy control, benign, moderate, severe) with regards to FSS average scores. To explore this possibility, the subjective illness severity slider of the experimental group was taken as the base for creating three severity groups according to the mean and standard deviation values of the slider. A healthy control group of participants that never had COVID-19 was also included in the classification of the severity groups.Consequently, a post-hoc test will be carried out to learn between which severity groups the significant differences existed.

Finally, to discover the largest influence that several psychological predictors have on Quality of Life a multiple linear regression using the "forward" method will be executed. That is, variables that could surface as influential, such as neuroticism and self-reported sleep quality, measured by the NEO-FFI and PSQI questionnaires respectively, will be inserted as additional predictors together with self-reported illness severity. The assumptions were assessed: Linearity, normality and homoscedasticity look in order and are met. In terms of multicollinearity, there seems to be no violations (FSS, QoL= 1, VIF= 1; self-reported sleep quality, QoL=.508, VIF=1.970; subjective illness severity, QoL=.781, VIF=1.280). In addition, correlations between subjective illness severity, subjective fatigue, neuroticism and self-reported sleep quality were examined. It was found that Quality of Life correlates significantly with three predictors (subjective illness severity: $r = -0.341$, $p<.01$; FSS: $r = -0.706$, $p<.01$; self-reported sleep quality: $r = -0.669$, $p<.01$) whereas it does not show a significant correlation with neuroticism ($r = -084$). Other correlations were found between self-reported sleep quality and subjective illness severity correlated significantly ($r =.258$, $p<.01$), neuroticism and subjective illness severity ($r = -0.171$,

$p<.05$), subjective fatigue and subjective illness severity ($r = .438$, $p<.01$) and self-reported sleep quality and subjective fatigue ($r = .754$, $p<.01$).

All of the following analyses will be carried out using IBM SPSS Statistics version 27 (IBM SPSS Statistics, New York, NY, United States). The Dutch and German datasets were exported from Qualtrics separately at first, to then form a merged dataset into SPSS. Moreover, to clarify what is intended for significant results, the golden standard of significance used in this thesis is a p value of .05.

Results

Subjective fatigue and COVID-19 diagnosis

The first assessment of this thesis regards the hypothesized positive relationship between COVID-19 diagnosis and higher FSS average scores. The independent-sample t-test revealed a difference of 2.3192, 95% CI [1.87 - 2,76], which is significant as it shows $t(218) = 10.234$, $p<.0001$ (Table 3), meaning that participants diagnosed with COVID-19 scored higher in the FSS questionnaire compared to the healthy control group, with a mean of $M=5.19$, $SD= 1.65$ against the $M=2.87$ and $SD= 1.42$ of the healthy control group.

Subjective illness severity and FSS average scores

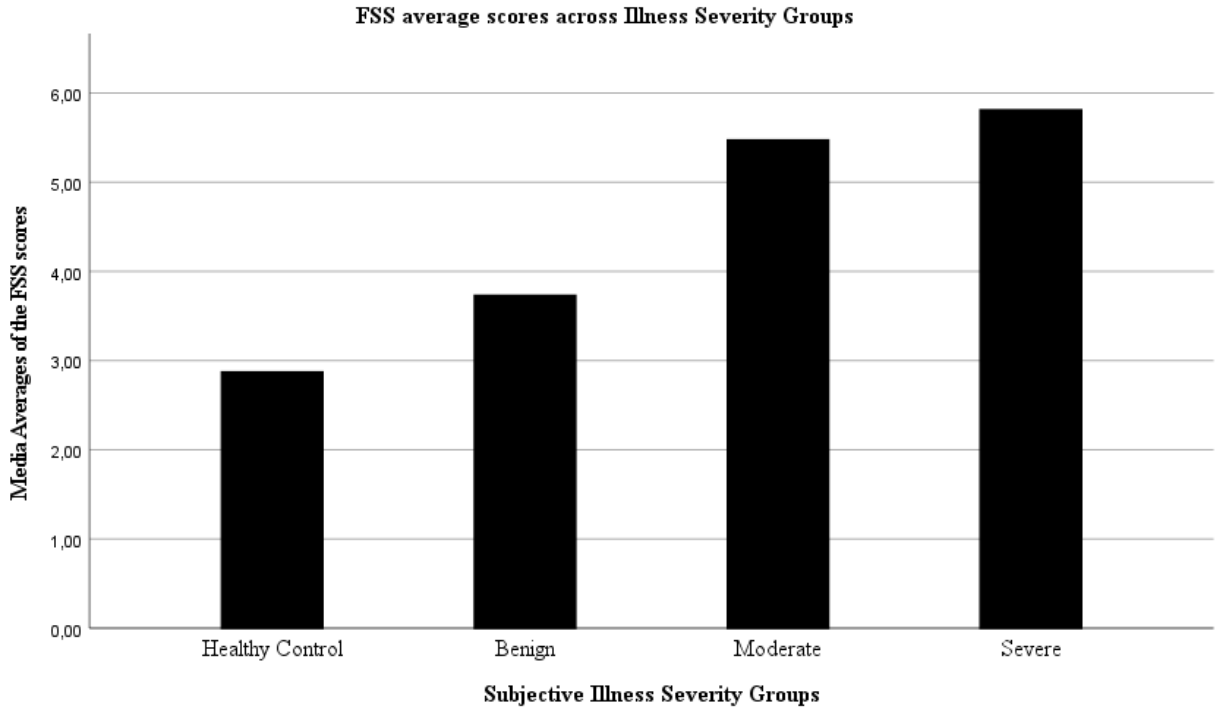
For the second analysis four severity groups were created according to the subjective illness severity slider. Given the great variability of values along the subjective illness severity slider, a division into four groups was considered by the author appropriate to delineate the different levels of severity.

Three of the four groups were determined by calculating the mean of the experimental group according to subjective illness severity (N=147) and subtract or add to it the SD, whereas the fourth group consisted of participants of the experimental group which did not experience symptoms (N=73). The mean of the experimental group was 55.97 whilst the standard deviation was 24.314. Thus, the approximated and ultimate division of the symptom severity groups was healthy control with no symptoms, benign with severity of symptoms ≤ 31, moderate with

values 32< x < 80 and finally severe, with symptom severity ≥81. First, Looking at the descriptives of the one-way ANOVA, it can be seen that the subjective fatigue averages scores of the four severity groups show a tendency to increase with self-reported illness severity (healthy control M=2.87 & SD=1.42, benign M=3.81 & SD=1.98, moderate M=5.47 & SD=1.37, severe M=5.8 & SD=1.24) (Figure 4). Moreover, the model shows a significant interaction effect between severity group and average FSS scores with a large effect size of [$F(3, 216) = 52.76$, $p<.0001$, $\eta^2=.42$]. This result indicates that at least one significant difference between the four severity groups. To know where exactly the significant relationships lie, a post-hoc test was performed. Four significant differences are detected by this test and they appear as follows: the means of the healthy control-moderate, healthy control-severe, benign-moderate and benign-severe comparisons are all significantly different between them, with $p<.001$.

Figure 3

Subjective Fatigue Average Scores across Severity Groups



Predictors of Quality of Life

Lastly, on the basis of evidence which suggests there could be a relationship between Quality of Life, subjective fatigue (Malik, 2021), sleep deprivation (Deserno, 2019) and neuroticism (Tananuvat, 2022), these three additional variables will be included in the regression as predictors, together with subjective illness severity. Correlations between subjective illness severity, subjective fatigue, neuroticism and self-reported sleep quality were examined. It was found that Quality of Life correlates significantly with three predictors (subjective illness severity: r = -0.341, p<.01; FSS: r = -0.706, p<.01; self-reported sleep quality: r = -0.669, p<.01) whereas it does not show a significant correlation with neuroticism (r = -084). Other correlations were found between self-reported sleep quality and subjective illness severity correlated significantly (r =.258, p<.01), neuroticism and subjective illness severity (r = -0.171, p<.05), subjective fatigue and subjective illness severity (r =.438, p<.01) and self-reported sleep quality and subjective fatigue (r =.754, p<.01).

The extent to which these predictors impacted Quality of Life was assessed in a multiple linear regression with the addition of the "forward" method. Using these three predictors 42.9% of the variance is explained (adjusted R^2=.429, [F(3, 143) = 37.553, p<.001, η^2= .55]. In the first step of this model, subjective fatigue has shown the biggest individual contribution to the Quality of Life outcome with a large adjusted R^2= .400, translating into 40% of explained variance. Continuing with the second model, adjusted R^2 increases to .423, or 42.3% of variance, adding self-reported sleep quality. In addition, both subjective fatigue (B= -3.889, SE= .392, t= -9.921, p<.001) and self-reported sleep quality (B= -2.352, SE=.903, t= -2.606, p<.000) significantly predict Quality of Life and show unique explanation of variance, whereas subjective illness

severity failed to significantly explain Quality of Life variance (B=-0.046, SE=.029, t=-1.560, p=.121).

Discussion

The objective of this study was to investigate the subjective dimension of fatigue in people who were affected by COVID-19 infection, to measure its severity according to gravity of COVID-19 symptoms experienced and to discover its impact on Quality of Life. It is essential to study subjective fatigue as it has been reported to be one of the most common, pervasive and long-lasting symptom experienced by the infected population (Islam, 2020; Mandal, 2021; Javad Koohsari, 2021) and one of the triggering factors for a decline in Quality of Life (Amato, 2020; Malik, 2021). It is clear that there are clinical implications to the study of subjective fatigue during this pandemic.

This discussion comprehends a summary of the procedures that took place in order to test the three aforementioned hypotheses, the interpretation of the results of the latter, some limitations that are worth noting, and finally the value of this article by means of future implications.

In order to test the hypotheses, it was first intended to overcome the ambiguity behind the characterization of subjective fatigue, relating this construct to the main questionnaire in use, the FSS. Apart from ensuring a relationship between subjective fatigue and COVID-19 diagnosis, a second inquiry was to discover a possible association between subjective fatigue severity and subjective illness severity. Remarkably enough, this path of research has not been investigated deeply yet, as explained by Dai et al. (2020). Finally, the relationship between subjective fatigue and another construct quantified in the COCO-19 test battery, namely Quality of Life was investigated. More specifically, the degree of influence of subjective fatigue on Quality of Life was explored.

Results obtained from this study are supportive of the first hypothesis, highlighting the presence of the virus as an influence for the level of subjective fatigue experienced by the participants affected by COVID-19. More specifically, subjective fatigue appeared to be significantly higher in the experimental group compared to the healthy control group. This development is perfectly in line with current, and past knowledge regarding fatigue and viral infections, adding to the final suggestion that indeed subjective fatigue is found to increase when a virus is diagnosed. Fatigue has undeniably been found to arise in great numbers in infected samples during this, and past, pandemic(s). In fact, fatigue was reported as one of the most common and potentially chronic symptoms during SARS, Ebola and Influenza A (Tansey et al., 2005; Magnus, 2015; Wilson, 2018). Similar results were found during SARS-CoV-2, as explained by Carfi (2020), del Rio (2020) and Davis et al. (2020).

Regarding the newly hypothesized positive link between severity of subjective fatigue and subjective illness severity, the results show that indeed the averages of subjective fatigue grow significantly. More precisely, an overall trend of more severe subjective fatigue is observed as the severity of the COVID-19 symptoms experienced by participants increased. The lowest subjective fatigue scores belong to the healthy control group, followed by the benign, moderate and severe groups, respectively. It is to be noted that several significant differences were found between the four severity groups. As a matter of fact, the healthy control group differs significantly from the moderate and severe groups. Similarly, the benign group has shown such a tendency, as it differs significantly from the moderate and severe groups as well. These findings not only suggest a brand new correlation between severity of subjective fatigue and subjective illness severity, but also display significant differences between subjectively stronger symptoms

to the presence of a milder course of the disease, as demonstrated by the significant differences between the benign group with the moderate and severe groups (Figure 4).

No significant differences were found between the adjacent groups of healthy control and benign groups, and moderate and severe groups. The former and latter non significant interaction results could signify that the experience of severe subjective fatigue will occur regardless whenever a certain threshold of subjective COVID-19 severity is overcomed. Consequently, once that threshold is surpassed, subjective fatigue will manifest as severe and will remain so, even without a significant growth. Assuming the threshold for significant levels of subjective fatigue to be 4.0 as explained by Enoka & Duchateau (2017), we can clearly see from Figure 3 that participants affected by COVID-19 will experience severe subjective fatigue in the early stages of a moderate severity of disease course. This implies that severe subjective fatigue appears not only in severe but also more moderate cases of the virus.

The latter finding is of great value for two reasons. First, previous attempts to draw correlational effects between severity of disease and severity of subjective fatigue were judged to be inconsistent (Tavahomi, 2021). The second reason involved the healthcare system, which has so far shown to be increasingly preoccupied with severe cases of infection, or at least with cases that required medical care (Huang et al., 2021). However, knowing that a pervasive symptom such as subjective fatigue manifests severely even in milder cases indicates the need of appropriate rehabilitation programs and other psychological interventions just as much as they are needed for more severe cases. In accordance with Bryson (2020) and Tavahomi (2021) it is relevant to implement interventions that can prevent the chronicity of certain symptoms post COVID-19.

Even more important, is the relationship between fatigue and other psychological variables. This final point leads to the last hypothesis of this study, formulated in order to discover the degree of influence that subjective fatigue has on Quality of Life, another vulnerable construct that has seen a decline during this pandemic (Bryson, 2020). Given the evidence provided by several authors, such as Amato (2020), Malik (2021) and Tabacof (2022), it is expected to find an association between subjective fatigue and Quality of Life. The results of the final analysis show that without doubts subjective fatigue contributes greatly in explaining Quality of Life outcomes. This analysis is perfectly in line with current research, and proves yet again the role of subjective fatigue in this pandemic.

Other variables were inserted in the final analysis, namely subjective illness severity, self-reported sleep quality and neuroticism. Results show that although a correlation between subjective illness severity and Quality of Life exists (Table 4), subjective illness severity does not display significant predictive influence over Quality of Life. As suggested by Hwang (2020) and Townsend (2021) Quality of Life outcomes happen irrespective of initial severity of COVID-19 infection. It can be inferred that perceived severity of symptoms is not a variable that contributes to the global decline of Quality of Life and that there might be other, perhaps more psychologically involved, variables to take into account to prevent poor Quality of Life. This finding additionally justifies the insertion of the remaining predictors. Moving to self-reported sleep quality, the multiple regression showed a significant explanation of variance. However significant, the contribution was very small compared with subjective fatigue influence, making self-reported sleep quality of subordinate impact. Nonetheless, this result seems in line with current research suggesting that sleep quality has an influence over Quality of Life. For instance, in a sample of non-clinical participants, poor sleep quality was moderately correlated with

Quality of Life in an Austrian sample (Zeitlhofer et al., 2000). Similarly, Andruskiene et al. found that self-reported sleep quality was associated with the overall worse indices of Quality of Life in a large sample (N=1602)(2008). Finally, analogous results were found by Baldwin et al. (2010) and Bower (2010). Unexpectedly, whilst the statistics revealed a correlation between subjective illness severity and self-reported sleep quality with Quality of Life, the association between neuroticism and Quality of Life was excluded by the model. In contrast with current knowledge, no correlation was found (Table 4). Quality of Life and neuroticism were found to be related in cases of Chronic Heart Failure (Samartzis, 2014), PD (Ma et al., 2018) and type-2 diabetes (Momeniarbat, 2017). This conflict of results could potentially stem from the difference in health conditions presented by the demographic data of the samples. Unlike the samples used by Samartzis (2014), Ma et al. (2018) and Momeniarbat (2017), the sample used in this study presented little incidence of comorbidities (Table 2), potentially causing disaccordance with other pre-existing findings.

Overall, this study suggests that participants who were diagnosed with COVID-19 experience subjective fatigue in greater severity compared to participants who never had the virus. A logical continuation of the study was to quantify the degree of subjective fatigue in the sample of participants affected by the viral infection. A correlational relationship was established between subjective fatigue and subjective illness severity, as these two constructs increased in severity simultaneously. To further delve into this relationship, mean differences between subjective fatigue of the four severity groups were examined in a post-hoc analysis. Significant differences exist between the means of the healthy control - benign groups, and the moderate - severe groups. Lastly, as suggested by previous research, a predictive influence of subjective fatigue was found with respect to Quality of Life, together with a secondary influence of

self-reported sleep quality and subjective illness severity, and the exclusion of the neuroticism personality trait from global prediction.

Limitations

Although this study positively supports the formulated hypotheses and contributes to current research trends regarding subjective fatigue and Quality of Life, it is important to recognize and to mention certain limitations. For once, a bias towards higher numbers of subjective fatigue severity is present in this study, and resides in the process of extraction of data from Qualtrics. It was found that the FSS likert scale of the Dutch sample was coded differently from manual rules. As explained in the method section, a simple algorithm was used to fix a coding error belonging to the Fatigue Severity Scales values of the Dutch sample, to comply with the manual rules of this questionnaire and run the statistical analyses. Unfortunately, this scaling method might have created a bias towards higher numbers, as every severity score number from zero to six increased apart from the 7's. It is therefore likely that subjective fatigue was overestimated in the Dutch sample, and for the threshold of 4.0 to be less meaningful. To compensate for the data pollution and bias, perhaps a change in significance threshold for subjective fatigue should have also taken place using the same algorithm. Even so, it was deemed too risky to alter the rule given by the FSS manual and in the end, the manual threshold of 4.0 was considered appropriate. An additional bias towards higher responses can be found in this study. Also, having a different nature, it can depend on the location of the FSS in the COCO-19 test battery. That led to a great number of participants (106) leaving the battery unfinished. As explained by Ackerman & Kanfer, lengthy tests show patterns of decline in general performance, and an increase in subjective fatigue (2009). It could be the case that the

position of the FSS might have amplified the feeling of fatigue and increased the average scores on the test, generating a bias towards more severe responses.

Moving to other variables, it is essential to mention subjective illness severity. This slider was created solely for the purpose of the COCO-19 research, and thus, it is not a standardized measure. Moreover, no indication as to what numbers on the slider referred to were provided to participants. This allowed participants to arbitrarily choose the severity of their symptoms on the slider as the interpretation of their symptomatic experience was not scaled nor objective, even when participants were affected by analogous symptoms. Moreover, three severity groups were created from the slider using the mean and standard deviation of the whole sample. However, these divisions are arbitrary, as they do not follow a specific rubric or a theoretically grounded method. Consequently, great variance between types of symptoms and their perceived severity is to be expected inside of the severity groups, creating an issue of reliability for the subjective illness severity variable. Still, this particular division of the severity groups were considered appropriate according to the great variability of symptom severity experienced by the participants.

Another limitation worth noting, is that the definition of subjective fatigue utilized in this research is a combination of the characterizations of fatigue given by Calabresi & Pitteri (2018) and Ortelli (2021), conceived by the author. A combination of definitions took place given the large collection of definitions available in research. This signifies that there is great variability in defining this construct, and different definitions of it are used according to the authors' needs. Obviously, the present original definition lacks standardization and scientific consent as well. This could mean that the final definition does not reflect completely the subjective experience of the participants given by the values of the Fatigue Severity Scale, and that the chance of

mismatching the validity of the definition with the values increases. However, this combination seemed to fit perfectly with all the domains present in the Fatigue Severity Scale questionnaire, which measures both mental, physical and interference instances, as seen in Table 2 (Enoka & Duchateau, 2017).

Future Implications

This study offers a mixture of confirmatory and novel data. For example, various secondary associations were reproduced, such as the positive relationship between subjective fatigue and COVID-19 already explored by (e.g.) Davis et al. (2020) and Lads (2020), and the influential weight of subjective fatigue on Quality of Life suggested by Tabacof (2022), amongst others. Novelty is found in the deeper exploration of the subjective illness severity variable in relation to subjective fatigue, representing a promising line of research from a practical perspective. The practicality of this original finding comes in demonstrating the importance of subjective fatigue, not only as an individual symptom, but also as a contributor to poor Quality of Life in this pandemic. In fact this study suggests a clear influence of subjective over Quality of Life. Likewise, previous authors such as Salawu et al. (2020) and Tabacof (2022) have suggested the same results in past and present pandemics, respectively. In addition to its high incidence, fatigue consistently appears to persist and debilitate the people affected by it (Malik, 2021).

Unlike the current medical approach to COVID-19 treatment, this study clearly draws more medical attention towards the so far neglected moderate cases of COVID-19 infections, as they appear to experience almost equal levels of severe subjective fatigue as the more severe cases. In fact, not only is subjective fatigue common, but it also influences work performance, productivity and general wellbeing (Taylor, 2019), as it induces states of reduced alertness and

reaction times (Folkhard, 2005). Even more significant for the healthcare system is the influence of subjective fatigue on Quality of Life. It has been shown that a decline in Quality of Life is a widespread phenomenon during pandemics (Bryson, 2020). Identifying factors that could lead to a decline in Quality of Life is essential to the population's wellbeing. As subjective fatigue might be one of them, it is necessary to catalyze the implementation of intervention programs that could prevent its chronicity and protect vulnerable aspects of daily living that could worsen Quality of Life. Future research should focus on identifying additional factors that expose Quality of Life to impairment, and to introduce new interventions adept to managing milder cases of infection.

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Appendix

Table 2

Fatigue Severity Scale Questionnaire

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