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Acute and chronic fatigue after COVID-19: The impact of depression and somatic distress

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ABSTRACT

Objective: Fatigue is the most frequent and burdensome symptom following COVID-19. The contribution of biopsychosocial factors remains unclear, particularly with respect to symptom duration. This exploratory study investigated the prevalence of acute and chronic fatigue after COVID-19 and examined biopsychosocial correlations.

Methods: Cross-sectional data from 452 participants of the Gutenberg Post-COVID Study were analyzed. All individuals had a previous Sars-CoV-2 infection. Participants were categorized into three groups (1) no fatigue during assessment, (2) fatigue lasting 1–<6 months at assessment, and (3) fatigue lasting 6 months or more at assessment. Fatigue was assessed using the Chalder Fatigue Questionnaire (CFQ) and classified as acute (<6 months) or chronic (≥ 6 months). The modified PHQ-9 (mPHQ-9, excluding the fatigue item) measured depressivity. SSD-12 measured the somatic symptom burden. Associations were examined using multivariable regression analyses.

Results: 51.6 % reported no fatigue, 13.9 % showed acute fatigue, 34.5 % displayed chronic fatigue. Vaccination status was not associated with fatigue. The severity of the infection was associated with acute fatigue. No significant associations were observed with chronic fatigue. When psychological variables (mPHQ-9, SSD-12) were introduced, associations with somatic pre-morbid conditions disappeared, except for body mass index. Higher levels of depressiveness and somatic distress increased the likelihood of both forms of fatigue, while lower social status was associated specifically with chronic fatigue.

Conclusion: Depressiveness and somatic distress are strongly linked to post-COVID fatigue, particularly its chronic form. These findings underscore the importance of a biopsychosocial framework and the need for interdisciplinary treatment approaches in post-COVID care.

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1. Introduction

Post-COVID-19 syndrome describes a range of symptoms persisting beyond the acute phase of SARS-CoV-2 infection, affecting a substantial proportion of both hospitalized and non-hospitalized individuals [1,2]. However, prevalence estimates vary widely due to differing methodologies, population characteristics, and diagnostic criteria, creating uncertainty about the true burden of the condition. The syndrome presents with high symptom variability—up to 200 distinct complaints have been described—and subtypes are currently under investigation [3]. Among the most frequently reported and functionally limiting symptoms is fatigue, which affects up to two-thirds of individuals with post-COVID-19 [4–6].

Fatigue is not specific to post-COVID and occurs across a wide range of somatic and psychological conditions, including cancer, inflammatory diseases, and affective disorders [7,8]. It is also a core symptom of major depressive episodes and frequently co-occurs with anxiety and somatic symptom disorders [9,10]. This considerable overlap complicates the interpretation of fatigue in post-COVID contexts [11]. Health insurance data from Germany highlight its relevance: fatigue is the leading cause of work absence among post-COVID patients [12]. It is associated with memory impairment and psychological symptoms such as anxiety and depression [11,13], and it ranks among the most common complaints in emergency and primary care settings—often without identifiable somatic etiology [8,14]. We defined acute fatigue as lasting 1–6 months, while chronic fatigue presents ≥6 months. This definition seems fitting as Post-COVID is defined as lasting 1–6 months, while Long-COVID as lasting ≥6 months.

Several risk factors for persistent post-COVID symptoms have been identified, including female sex, older age, somatic comorbidities, and psychological vulnerability [15–17]. However, most studies treat fatigue as a unitary construct. Little is known about how these risk factors relate to the duration of fatigue—particularly the distinction between acute and chronic forms, which may have different implications for treatment and prognosis. It also remains unclear whether persistent fatigue reflects direct sequelae of infection, the psychosocial burden of the pandemic, or the amplification of pre-existing health problems [18].

The aim of the present study is to identify sociodemographic, somatic, and psychological factors associated with acute (1–6 months) and chronic fatigue (≥6 months) following COVID-19. Rather than addressing causality or etiology, this study examines associative patterns within a large, well-characterized post-COVID cohort. Given the known comorbidity of fatigue and depression, we specifically focus on depressiveness and somatic distress, hypothesizing that these factors exhibit particularly strong associations with chronic fatigue—potentially exceeding the influence of infection severity.

2. Patients & methods

2.1. Sample

The data set is part of the Gutenberg Post-COVID Study conducted at the University Medical Center Mainz. We recruited based on a prior SARS-CoV-2 infection confirmed by PCR testing, including both hospitalized and non-hospitalized individuals. Due to character of viral infections, the exact on-set of the infection could not be assessed. Trained physicians systematically assessed the patients according to predefined study protocols. This included a medical examination, extended anamnesis as well as self-reported questionnaires regarding the current somatic and psychological symptoms. If necessary, a referral to a medical specialist was ordered. The results were included in the database. No previous health record or insurance data is included. Based on the literature, we compiled a list of the most common comorbidities.

At the time of assessment, the Gutenberg Post-COVID Study included 479 participants. Sufficient knowledge of the German language and being over the age of 18 were defined as inclusion criteria. Additionally, because the primary focus of this study was measuring and investigating fatigue, participants with missing data on the Chalder Fatigue Scale were removes. This yielded a final analysis sample of $n = 452$.

The current sample was categorized into three subgroups: (1) no fatigue during assessment, (2) individuals with fatigue lasting 1–<6 months at the moment of assessment, and (3) individuals with chronic fatigue lasting 6 months or more at the time of assessment.

The study was conducted in accordance with the Declaration of Helsinki and adhered to the principles of Good Clinical and Epidemiological Practice. Ethical approval was obtained from the local ethics committee of the Landesärztekammer Rheinland-Pfalz (approval number: 2021–16,221).

2.2. Measures

Target symptoms in the study cohort were assessed using validated self-report questionnaires. Fatigue, the primary outcome variable, was measured using the Chalder Fatigue Questionnaire (CFQ) [19,20]. Therefore the CFQ reflects the symptom level at the time of assessment. To address the temporal aspect, participants additionally reported the onset and duration of their fatigue symptoms, which allowed us to distinguish between acute (≤ 6 months) and chronic (> 6 months) fatigue. The self-administered 11-item questionnaire inquired about several aspects of fatigue including feeling weak, lacking energy, having to rest more, and having difficulties concentrating on a yes or no scale. Additionally, the respondents were asked about the duration of the problems. If respondents reported less than four symptoms to be present, they were categorized as having no fatigue. If respondents reported four or more than four symptoms to be present for a duration of less than six months, they were categorized as having fatigue. Lastly, if the respondents reported four or more than 4 symptoms for a duration of at least 6 months, they are categorized as chronically fatigued.

Next, we assessed psychological instruments. The Patient Health Questionnaire (PHQ-9) is a reliable and valid 9-item questionnaire for depressive symptoms. In order to avoid overlap, we excluded the fatigue item of PHQ-9, turning it into an eight-item version of the scale [21–23]. Therefore, we refer to the questionnaire as mPHQ-9, indicating that we applied a modified PHQ-9. Anxiety was assessed with seven item questionnaire Generalized Anxiety Disorder Screener (GAD-7) [24,25] and loneliness with the three-item version of the UCLA Loneliness Scale [26,27]. The psychological features of the somatic symptom disorder were assessed using the 12-item Somatic Symptom Disorder Scale (SSD-12) [28,29]. The EUROHIS-QOL measures the general quality of life using 8 items [30,31].

Additionally, we inquired about somatic pre-morbid conditions by asking the respondents if they have been previously diagnosed with any of the following illnesses: atrial fibrillation, heart failure, coronary heart disease, myocardial infarction, endocarditis, myocarditis, stroke, diabetes, hypertension, cancer, asthma, COPD, sleep apnoea, inflammatory disease of the central nervous system. Subsequently, a dichotomous variable was formed indicating if a respondent had any of the mentioned somatic pre-morbid conditions or not. We also inquired about height and weight and calculated the respective body mass index (BMI) of each respondent. Health behaviour such as smoking or alcohol consumption, as well as the intake of medications (such as opioids, antidepressants, antipsychotics, or psychostimulants) were assessed. Regarding COVID-19 specific variables, we inquired if the respondents were vaccinated (yes/no), the severity of their worst infection (no symptoms, mild symptoms, moderate symptoms, severe symptoms), as well as the length of sick leave the respondents took. Lastly, we also inquired about sociodemographic information, such as sex, age, and socioeconomic status (SES). SES was assessed using a composite index, following the approach by Lampert and Kroll. The index equally weights three components: (1) education level, (2) occupational status, and (3) equivalized household income. Each component is scored from 1 (low) to 7 (high), resulting in a total SES score ranging from 3 to 21, with higher values indicating

higher socioeconomic status.

3. Methods

First, descriptive statistics were calculated to characterize the sample. Absolute and relative frequencies were reported for categorical

Table 1
Sociodemographic information of the total sample ($N = 452$) and the respective fatigue groups.

	Complete data	Total sample	No Fatigue (CFS < 4)	Acute Fatigue (CFS ≥ 4 & < 6 months)	Chronic Fatigue (CFS ≥ 4 & ≥ 6 months)	p (1–2)	p (1–3)	p (2–3)
N	452	452	233	63	156			
Sociodemographic information								
Sex (male)	452	197 (43.6 %)	127 (54.5 %)	20 (31.7 %)	50 (32.1 %)	**0.002**	**<0.001.**	1.000
Age	452	53.16 (15.21)	54.59 (15.01)	51.97 (17.12)	51.52 (14.59)	0.445	0.125	0.979
SES	452	14.44 (3.94)	15.07 (3.87)	13.71 (4.16)	13.80 (3.82)	**0.038**	**0.005**	0.988
Pre-existing conditions								
Somatic pre-morbid conditions (yes)	452	226 (50.0 %)	100 (42.9 %)	26(41.3 %)	100 (64.1 %)	0.927	**<0.001**	**0.003**
Atrial fibrillation	452	13 (2.9 %)	4 (1.7 %)	2 (3.2 %)	7 (4.5 %)	0.822	0.192	0.947
Heart failure	452	18 (4.0 %)	5 (2.1 %)	2 (3.2 %)	11 (7.1 %)	0.992	**0.033**	0.433
Coronary heart disease	452	20 (4.4 %)	12 (5.2 %)	1 (1.6 %)	7 (4.5 %)	0.380	0.954	0.524
Myocardial infarction	452	9 (2.0 %)	6 (2.6 %)	0 (0.0 %)	3 (1.9 %)	0.434	0.940	0.641
Endocarditis	452	1 (0.2 %)	0 (0.0 %)	0 (0.0 %)	1 (0.6 %)	1.000	0.840	1.000
Myocarditis	452	12 (2.7 %)	4 (1.7 %)	3 (4.8 %)	5 (3.2 %)	0.345	0.540	0.874
Stroke	452	6 (1.3 %)	3 (1.3 %)	0 (0.0 %)	3 (1.9 %)	0.844	0.937	0.641
Diabetes	452	38 (8.4 %)	17 (7.3 %)	7 (11.1 %)	14 (9.0 %)	0.469	0.683	0.816
Hypertension	452	149 (33.0 %)	70 (30.0 %)	15 (23.8 %)	64 (41.0 %)	0.416	**0.034**	**0.025**
Cancer	452	51 (11.3 %)	23 (9.9 %)	5 (7.9 %)	23 (14.7 %)	0.824	0.194	0.253
Asthma	452	52 (11.5 %)	11 (4.7 %)	7 (11.1 %)	34 (21.8 %)	0.113	**<0.001**	0.100
COPD	452	9 (2.0 %)	1 (0.4 %)	3 (4.8 %)	5 (3.2 %)	**0.043**	0.079	0.874
Sleep Apnea	452	33 (7.3 %)	8 (3.4 %)	5 (7.9 %)	20 (12.8 %)	0.230	**0.001**	0.427
Inflammatory disease of the central nervous system	452	2 (0.4 %)	1 (0.4 %)	0 (0.0 %)	1 (0.6 %)	1.000	1.000	1.000
BMI (mean)	452	27.75 (5.85)	26.74 (4.39)	28.22 (7.43)	29.05 (6.74)	0.168	**<0.001**	0.599
Smoking ever (yes)	441	187 (42.4 %)	98 (43.4 %)	23 (37.7 %)	66 (42.9 %)	0.517	1.000	0.591
Alcohol consumption								
on weekends (yes)	370	210 (56.8 %)	127 (61.7 %)	26 (51.0 %)	57 (50.4 %)	0.263	0.146	0.797
on weekdays (yes)	369	95 (25.7 %)	62 (30.1 %)	12 (23.5 %)	21 (18.7 %)	0.566	**0.046**	0.247
Medication								
Opioids (yes)	443	11 (2.5 %)	1 (0.4 %)	3 (5.2 %)	7 (4.6 %)	**0.032**	**0.015**	1.000
antidepressants (yes)	443	42 (9.5 %)	3 (1.3 %)	6 (10.3 %)	33 (21.6 %)	**0.002**	**<0.001**	0.094
antipsychotics (yes)	443	14 (3.2 %)	5 (2.2 %)	2 (3.4 %)	7 (4.6 %)	0.924	0.300	1.000
psychostimulants (yes)	443	43 (9.7 %)	3 (1.3 %)	6 (10.3 %)	34 (22.2 %)	**0.002**	**<0.001**	0.077
Psychological variables								
Chalder Fatigue Scale (CFS)	452	4.36 (3.51)	1.29 (0.73)	6.57 (1.90)	8.04 (1.97)	**<0.001**	**<0.001**	**<0.001**
Depression (mPHQ-9)	452	4.85 (3.90)	2.54 (2.09)	5.66 (3.05)	7.96 (4.00)	**<0.001**	**<0.001**	**<0.001**
Anxiety (GAD7)	452	4.21 (3.74)	2.56 (2.40)	4.72 (3.49)	6.46 (4.23)	**<0.001**	**<0.001**	**0.001**
Quality of Life (EUROHIS-QOL)	452	28.11 (2.90	28.99 (2.69)	27.89 (2.37)	26.87 (2.94)	**0.013**	**<0.001**	**0.034**
Loneliness (UCLA)	451	2.88 (2.40)	2.13 (1.83)	2.91 (2.39)	3.96 (2.72)	**0.040**	**<0.001**	**0.005**
Somatic symptoms (SSD-12)	452	11.62 (10.54)	6.03 (6.70)	12.76 (8.01)	19.49 (10.97)	**0.000**	**<0.001**	**<0.001**
COVID-19 related variables								
SARS-CoV-2 vaccination (yes)	428	418 (97.7 %)	214 (96.8 %)	57 (100.0 %)	147 (98.0 %)	0.375	0.723	0.671
Severity of worst Sars-CoV-2 infection	334							
no symptoms		35 (10.5 %)	27 (16.2 %)	4 (8.9 %)	4 (3.3 %)	0.316	**0.001**	0.267
mild symptoms		61 (18.3 %)	43 (25.9 %)	5 (11.1 %)	13 (10.6 %)	0.058	**0.002**	1.000
moderate symptoms		139 (41.6 %)	66 (39.8 %)	23 (51.1 %)	50 (40.6 %)	0.231	0.975	0.300
severe symptoms		99 (29.6 %)	30 (18.1 %)	13 (28.9 %)	56 (45.5 %)	0.165	**<0.001**	0.078
Sick days within <3 months after infection (mean)	368	12.23 (24.25)	7.19 (19.76)	9.17 (14.08)	21.07 (30.61)	0.849	**<0.001**	**0.005**
Sick days within 3–6 months after infection (mean)	319	8.39 (29.07)	3.25 (13.17)	3.50 (6.87)	18.45 (45.73)	0.998	**<0.001**	**0.008**
Sick days within >6 months after infection (mean)	339	13.60 (39.92)	5.65 (19.50)	18.13 (63.89)	24.33 (48.00)	0.127	**<0.001**	0.632

Note. Significant *p*-values marked. Complete data indicates the number of respondents of which data was available. P (1–2), p (1–3), and p (2–3) indicate the significance of the comparisons between groups 1 and 2, groups 1 and 3, and groups 2 and 3, respectively.

variables, while means and standard deviations were used for continuous variables. Prior to inferential testing, we assessed the normality of continuous variables. In order to test for significant differences between the fatigue groups, we either used chi-square tests (for categorical variables) or *t*-tests with Bonferroni correction to adjust for multiple comparisons (for continuous variables). Prior to the t-tests, we checked if the assumption of normal distribution was met by examining the data using the Shapiro-Wilk test. In the case of non-normally distributed variables, we additionally applied non-parametric tests (Mann-Whitney U for two-group comparisons and Kruskal-Wallis tests for three-group comparisons) to assess if the results from the t-tests upheld. All t-test results were confirmed by the non-parametric tests.

The primary analysis employed multinomial logistic regression models to examine associations between group membership (no fatigue, fatigue, and chronic fatigue) with individuals without fatigue set as the reference category. Three sequential models were constructed to explore the incremental effect of different covariates: Model 1 included sociodemographic variables (sex, age, and socioeconomic status); Model 2 additionally adjusted for somatic pre-morbid conditions (dichotomous), body mass index (BMI), and smoking status; Model 3 further incorporated psychological measures including depressiveness, anxiety, quality of life, loneliness, and somatic symptoms.

Odds ratios (ORs) with 95 % confidence intervals (CIs) were estimated to quantify the strength and precision of associations. A two-sided *p*-value <0.05 was considered statistically significant. To ensure robustness, a sensitivity analysis was performed including hospitalized SARS-CoV-2 infection as an additional predictor. All calculations were performed using R version 4.1.1 [32,33].

4. Results

A total of 452 participants provided complete data and were included in the final analysis. 27 (5.6 %) participants had an incomplete dataset. The mean age was 53.16 years (± 15.21). The sample included slightly more women than men, with 43.4 % of participants identifying as male. Participants differed in terms of post-COVID fatigue duration: a majority reported no fatigue (51.6 %, $n = 233$), while 13.9 % ($n = 63$) reported fatigue lasting 1– < 6 months, and 34.5 % ($n = 156$) reported chronic fatigue lasting six or more than 6 months. Notably, the group without fatigue (n = 233) served as the reference group for all subsequent analyses. Table 1 displays the descriptive characteristics of the total sample and the three fatigue subgroups.

Respondents without fatigue were significantly more likely to be male and reported the highest SES, whereas individuals with chronic fatigue reported the lowest SES. Participants with chronic fatigue also had the highest mean BMI and were more likely to use opioids, antidepressants, or psychostimulants. They reported the highest levels of depressive symptoms, somatic distress, and loneliness, as well as the lowest scores in quality of life.

Subsequently, positive and negative associations fatigue were examined using logistic regression models (see Table 2). In the initial model including only sociodemographic factors, female sex was strongly associated with both fatigue and chronic fatigue. Specifically, being female more than doubled the odds of reporting chronic fatigue. Higher SES was associated with a lower likelihood of fatigue in both categories.

In the second model, which included health-related variables (BMI, smoking, somatic comorbidities), higher BMI significantly increased the odds of fatigue ($p = 0.038$) and chronic fatigue ($p = 0.004$). Pre-existing somatic conditions were significantly associated with chronic ($p < 0.001$) but not acute fatigue. Conversely, increasing age appeared to reduce the odds for chronic fatigue.

In the third model, which additionally included psychological variables (mPHQ-9 and SSD-12), most previously significant associations diminished, with the exception of BMI. Both depressive symptoms and somatic distress remained highly significant associations with fatigue status ($p < 0.001$). For example, a one-point increase in SSD-12 score increased the odds of reporting chronic fatigue by 9 %, even after controlling for other factors. These results underline the dominant role of psychological burden in post-COVID fatigue.

To further explore the role of infection severity, a sensitivity analysis was conducted using a subgroup of participants with available clinical severity indicators (e.g., hospitalization, oxygen requirement). In this subgroup, infection severity was associated with acute fatigue but showed no association with chronic fatigue. These findings clarify the earlier summary: while infection severity appears relevant for short-term fatigue, it does not explain symptom persistence beyond six months (see Table 3).

5. Discussion

This study reveals distinct associations between symptom duration and biopsychosocial factors. Notably, psychological and social factors, particularly depressiveness and somatic distress, showed higher odds of having chronic fatigue than acute forms or biological variables.

The key finding is that depressive symptoms and somatic burden were the strongest independent association of both acute and chronic fatigue, with the most pronounced effects seen in chronic fatigue. Somatic distress, as defined by Pignon et al., comprises three components: (1) persistent and excessive concern about symptoms, (2) sustained health-related anxiety, and (3) disproportionate time and energy devoted to health concerns. These features likely promote symptom amplification and chronicity through dysfunctional attentional and behavioral patterns.

Importantly, social variables also contributed to chronic fatigue. Lower socioeconomic status and greater loneliness were significantly associated with chronic fatigue, while higher SES appeared to buffer against symptom persistence. These associations were not evident in acute fatigue, suggesting a more prominent role for psychosocial vulnerability in the chronification of symptoms.

Biological factors such as female sex, higher BMI, and the use of psychotropic medication were associated with fatigue. However, once psychological variables were included, their association diminished—with the exception of BMI. The severity of the acute infection, in contrast, was related only to acute fatigue and were not independently associated with chronic fatigue.

Crucially, our findings challenge the assumption that infection severity is the primary driver of long-term fatigue. While initial illness severity may contribute to transient fatigue, chronic symptoms appear more closely tied to psychological and social processes. This underscores the relevance of the biopsychosocial model [34,35] in understanding post-COVID fatigue.

These findings can also be interpreted within the predictive coding framework. According to this theory, chronic symptoms arise when the brain prioritizes top-down expectations over incoming interoceptive input. As proposed by Löwe et al. [36], individuals with heightened health anxiety and somatic preoccupation may experience persistent fatigue due to the reinforcement of maladaptive symptom predictions. This model offers a compelling explanation for the strong influence of psychological variables in our study.

To our knowledge, this is the first study to systematically differentiate between acute and chronic post-COVID fatigue and relate them to biopsychosocial factors in a large, well-characterized cohort. Previous studies have demonstrated links between fatigue and affective symptoms [11,13], but few have explored differences by symptom duration. Our findings suggest that chronic fatigue is associated with a distinct vulnerability profile, with psychological and social components playing a particularly prominent role.

Finally, our results are consistent with earlier work showing that fatigue is often not attributable to somatic disease alone [8,14]. Instead, it emerges as a transdiagnostic symptom shaped by emotional regulation, attentional focus, and psychosocial context [7,9,37]. In conclusion, our findings highlight the central role of psychological and somatic

Table 2
Multinominal logistic regressions.

	Model 1				Model 2				Model 3			
	N = 452				*N* = 440				*N* = 439			
	Acute Fatigue		Chronic fatigue		Acute Fatigue		Chronic fatigue		Acute Fatigue		Chronic fatigue	
	OR [95 % CI]	p	OR [95 % CI]	p	OR [95 % CI]	p	OR [95 % CI]	p	OR [95 % CI]	p	OR [95 % CI]	p
Sex (Ref. male)	2.394 [1.316–4.356]	**0.004**	2.346 [1.522–3.616]	**<0.001**	2.750 [1.483–5.101]	**0.001**	2.776 [1.749–4.406]	**<0.001**	1.675 [0.842–3.333]	0.142	0.175 [0.627–2.200]	0.615
Age	0.989 [0.970–1.008]	0.245	0.987 [0.973–1.001]	0.068	0.988 [0.968–1.009]	0.265	0.973 [0.958–0.989]	**0.001**	0.996 [0.973–1.019]	0.722	0.990 [0.969–1.011]	0.341
SES	0.912 [0.847–0.982]	**0.014**	0.916 [0.867–0.967]	**0.002**	0.922 [0.856–0.994]	**0.034**	0.929 [0.877–0.985]	**0.013**	0.956 [0.880–1.039]	0.291	0.994 [0.920–1.075]	0.884
Somatic pre-morbid conditions					0.988 [0.521–1.876]	0.972	2.841 [1.744–4.626]	**<0.001**	0.767 [0.374–1.572]	0.468	1.840 [0.955–3.547]	0.069
BMI					1.057 [1.003–1.114]	**0.038**	1.062 [1.019–1.107]	**0.004**	1.065 [1.001–1.133]	**0.046**	1.054 [0.994–1.117]	0.077
Smoking ever					0.794 [0.434–1.454]	0.455	0.949 [0.601–1.498]	0.821	0.611 [0.309–1.210]	0.157	0.630 [0.335–1.186]	0.152
Depressiveness (mPHQ-9)									1.475 [1.244–1.748]	**<0.001**	1.739 [1.479–2.046]	**<0.001**
Anxiety (GAD-7)									0.986 [0.856–1.136]	0.848	0.966 [0.849–1.101]	0.607
Quality of Life (EURHOHIS-QOL)									0.974 [0.850–1.115]	0.699	0.939 [0.831–1.062]	0.315
Loneliness (UCLA)									0.921 [0.778–1.090]	0.339	0.945 [0.813–1.100]	0.466
Somatic symptoms (SSD-12)									1.063 [1.016–1.113]	**0.008**	1.095 [1.050–1.141]	**<0.001**

Note. Reference for each model is no fatigue (CFS < 4). OR = odds ratio, CI = 95 % confidence interval, p = p-value, SES = socioeconomic status, BMI = body mass index.

Table 3
Multinominal logistic regression (sensitivity analysis with symptom severity).

	Model 1				Model 2				Model 3			
	N = 452				N = 440				*N* = 326			
	Acute Fatigue		Chronic fatigue		Acute Fatigue		Chronic fatigue		Acute Fatigue		Chronic fatigue	
	OR [95 % CI]	p	OR [95 % CI]	p	OR [95 % CI]	p	OR [95 % CI]	p	OR [95 % CI]	p	OR [95 % CI]	p
Sex (Ref. male)	2.394 [1.316–4.356]	**0.004**	2.346 [1.522–3.616]	**<0.001**	2.750 [1.483–5.101]	**0.001**	2.776 [1.749–4.406]	**<0.001**	2.084 [0.907–4.789]	0.084	1.302 [0.639–2.654]	0.468
Age	0.989 [0.970–1.008]	0.245	0.987 [0.973–1.001]	0.068	0.988 [0.968–1.009]	0.265	0.973 [0.958–0.989]	**0.001**	0.981 [0.952–1.010]	0.200	0.996 [0.971–1.022]	0.773
SES	0.912 [0.847–0.982]	**0.014**	0.916 [0.867–0.967]	**0.002**	0.922 [0.856–0.994]	**0.034**	0.929 [0.877–0.985]	**0.013**	0.948 [0.856–1.050]	0.308	0.995 [0.909–1.088]	0.909
Somatic pre-morbid conditions					0.988 [0.521–1.876]	0.972	2.841 [1.744–4.626]	**<0.001**	0.602 [0.255–1.421]	0.247	1.710 [0.816–3.582]	0.155
BMI					1.057 [1.003–1.114]	**0.038**	1.062 [1.019–1.107]	**0.004**	1.060 [0.989–1.136]	0.097	1.030 [0.966–1.097]	0.366
Smoking ever					0.794 [0.434–1.454]	0.455	0.949 [0.601–1.498]	0.821	0.586 [0.254–1.350]	0.209	0.595 [0.288–1.229]	0.161
Severe infection (yes)									1.122 [0.452–2.784]	0.804	1.738 [0.811–3.724]	0.155
Depressiveness (mPHQ-9)									1.399 [1.143–1.712]	**0.001**	1.658 [1.378–1.994]	**<0.001**
Anxiety (GAD-7)									0.993 [0.850–1.160]	0.931	0.962 [0.834–1.109]	0.589
Quality of Life (EURHOHIS-QOL)									0.968 [0.815–1.151]	0.716	0.897 [0.776–1.036]	0.140
Loneliness (UCLA)									0.943 [0.774–1.149]	0.559	0.882 [0.738–1.055]	0.170
Somatic symptoms (SSD-12)									1.069 [1.008–1.133]	**0.025**	1.102 [1.046–1.160]	**<0.001**

Note. Reference for each model is no fatigue (CFS < 4). OR = odds ratio, CI = 95 % confidence interval, p = p-value, SES = socioeconomic status, BMI = body mass index.

distress in post-COVID fatigue and emphasize the need for integrative, multidisciplinary approaches to diagnosis and treatment.

6. Limitations

Several limitations must be considered. First, the cross-sectional, exploratory design does not allow causal inference. While associations between fatigue and depressive symptoms were robust, we cannot determine directionality. Future longitudinal studies are needed to clarify temporal relationships.

Second, our definition of acute fatigue (1–6 months) differs from some prior classifications that define acute fatigue as <1 month. This may limit comparability. Additionally, fatigue was measured at the time of assessment Therefore it is unclear whether the acute fatigue group merely represents an earlier phase of symptom development that will evolve into chronic fatigue. Longitudinal follow-up will be essential to distinguish transient from persistent trajectories.

Third, although the sample size is substantial, some subgroups were relatively small, and certain covariates (e.g., comorbidities) were not available in full granularity. Nonetheless, the cohort is well-characterized, and few post-COVID studies offer this level of depth and breadth in a single sample.

Fourth, we lacked data on participants' fatigue status prior to infection as well as a clear date for the onset of infection. This is a key limitation, as we cannot rule out pre-existing fatigue symptoms that may have been amplified by the infection.

Fifth, we did not include a healthy control group. However, comparisons were made across post-COVID individuals with and without fatigue, which may offer a more clinically relevant contrast than comparisons with uninfected individuals. This approach aligns with recommendations to use “high-level” control groups in post-infectious symptom research.

Finally, fatigue is a highly multifactorial construct influenced by numerous biological, psychological, behavioral, and social variables. While our study considered a broad range of relevant factors, several potentially important influences—such as physical activity levels, sleep patterns, and inflammatory biomarkers - should be incorporated in future studies to provide a more comprehensive understanding.

CRediT authorship contribution statement

Kamiar K. Rückert: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Julia Petersen:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Philipp S. Wild:** Writing – review & editing, Supervision, Conceptualization. **Thomas Münzel:** Writing – review & editing, Supervision, Conceptualization. **Jochem König:** Writing – review & editing, Conceptualization. **Karl J. Lackner:** Writing – review & editing, Supervision, Conceptualization. **Isabel Heinrich:** Writing – review & editing, Conceptualization. **Julia Weinmann-Menke:** Writing – review & editing, Conceptualization. **Christian Dresel:** Writing – review & editing, Conceptualization. **Marc Bodenstein:** Writing – review & editing. **Michael Kreuter:** Writing – review & editing, Conceptualization. **Felix Rausch:** Writing – review & editing, Methodology, Conceptualization. **Manfred E. Beutel:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Jasmin Ghaemi Kerahrodi:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

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