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Research paper

Depression and fatigue six months post-COVID-19 disease are associated with overlapping symptom constellations: A prospective, multi-center, population-based cohort study

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ABSTRACT

Background: Depression and fatigue are commonly observed sequelae following viral diseases such as COVID-19. Identifying symptom constellations that differentially classify post-COVID depression and fatigue may be helpful to individualize treatment strategies. Here, we investigated whether self-reported post-COVID depression and post-COVID fatigue are associated with the same or different symptom constellations.
Methods: To address this question, we used data from COVIDOM, a population-based cohort study conducted as part of the NAPKON-POP platform. Data were collected in three different German regions (Kiel, Berlin, Würzburg). We analyzed data from >2000 individuals at least six months past a PCR-confirmed COVID-19 disease, using elastic net regression and cluster analysis. The regression model was developed in the Kiel data set, and externally validated using data sets from Berlin and Würzburg.
Results: Our results revealed that post-COVID depression and fatigue are associated with overlapping symptom constellations consisting of difficulties with daily activities, perceived health-related quality of life, chronic exhaustion, unrestful sleep, and impaired concentration. Confirming the overlap in symptom constellations, a

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follow-up cluster analysis could categorize individuals as scoring high or low on depression and fatigue but could not differentiate between both dimensions.
Limitations: The data presented are cross-sectional, consisting primarily of self-reported questionnaire or medical records rather than biometric data.
Conclusions: In summary, our results suggest a strong link between post-COVID depression and fatigue, highlighting the need for integrative treatment approaches.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has had a profound worldwide impact, resulting in millions of confirmed cases and deaths globally. Attention has now turned to the long-term effects of COVID-19, since about every tenth person infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may suffer from a sequela called post-acute COVID-19 syndrome, or post-COVID (Nalbandian et al., 2021). These patients experience symptoms for >12 weeks after infection (Greenhalgh et al., 2020), some of them even more severe than during the initial infection (Al-Aly et al., 2021). Shortness of breath, fatigue or insomnia as well as depression are common symptoms within the first six months after SARS-CoV-2 infection (Renaud-Charest et al., 2021; Titze-de-Almeida et al., 2022; Taquet et al., 2021).

Depression is characterized by persistent feelings of sadness, hopelessness, and lack of interest. It impairs daily life and overall well-being of those affected and is commonly treated with medication and psychotherapy (Beck and Alford, 2009). The COVID-19 pandemic has led to an increase in depression cases, including post-COVID depression (Mazza et al., 2022). Risk factors associated with post-COVID depression include sex (with a higher incidence in females), a history of psychiatric symptoms, psychiatric symptoms one month after discharge from the hospital when treated for COVID-19, systemic inflammation during the acute infection phase, as indicated by multiple biomarkers, and COVID symptom severity (Bahmer et al., 2022; Renaud-Charest et al., 2021). Renaud-Charest et al. (2021) reported in a review that 11 to 28 % of individuals reported symptoms of depression at least 12 weeks after the confirmed SARS-CoV-2 infection, with clinically significant symptoms of depression ranging from 3 to 12 %. Similar to the treatment of conventional depression, cognitive behavioral therapy and antidepressants are proposed as therapeutic interventions, although controlled studies are lacking (Al-Alawi et al., 2021).

Fatigue is characterized by a feeling of tiredness, exhaustion, and lack of energy. Typically, the loss of energy cannot be regained by increasing periods of rest and may have a significant impact on a person's ability to cope with activities of daily living. The origins of fatigue are multifaceted, including cognitive dysfunction, imbalance in neurotransmitter levels, psychiatric disorders, or psychosocial burden (Afari and Buchwald, 2003). Various predisposing variables associated with post-COVID fatigue have been reported, including older age, female sex, duration of disease recovery from COVID-19 and disease severity (Rudroff et al., 2020; Joli et al., 2022; Bahmer et al., 2022). A comprehensive and systematic review and meta-analysis by Ceban et al. (2022) showed that approximately a third of both hospitalized and non-hospitalized patients suffered from persistent fatigue, and a fifth from cognitive impairment at least 12 weeks following the COVID-19 diagnosis. Recent studies also analyzing data from COVIDOM, the population-based cohort study which is used in the present research, showed that fatigue is among the most frequent persisting symptoms 6–12 months after SARS-CoV-2 infection (Bahmer et al., 2022) and is discernable from post-COVID cognitive impairments (Hartung et al., 2022). Empirical evidence for the success of therapeutic interventions targeting post-COVID fatigue is scarce and predominantly stems from small and uncontrolled studies focusing on restoring respiratory function as one of the major impairments (Joli et al., 2022). Studies on fatigue associated with cancer treatment and other viral infections revealed positive effects of psychostimulants (Tomlinson et al., 2018), while the effects of selective serotonin reuptake inhibitors (SSRIs) were rather inconsistent (Wearden et al., 1998). In addition, cognitive behavioral therapy has been successfully used to treat chronic fatigue syndrome, particularly in cases of comorbid depression and anxiety disorders (Castell et al., 2011).

Fatigue and depression are often characterized as distinct entities. However, in practice they often occur in concert and distinguishing them can be challenging (Afari and Buchwald, 2003; Leone, 2010). Thus, it is still unclear if post-COVID depression and post-COVID fatigue should be treated as separate syndromes or as concomitant disease with integrative treatments. Evidence that links post-COVID depression and fatigue to different symptom constellations would favor fatigue or depression-specific treatment schemes. In contrast, a large overlap in variables associated with post-COVID depression and fatigue would support integrative approaches combining fatigue and depression-specific treatment features. In this study, we assessed if self-reported post-COVID depression and fatigue are related to different or the same symptom constellations.

2. Patients & methods

2.1. Sample

Data sets were retrieved from COVIDOM, within the population-based cohort platform (POP) of the German National Pandemic Cohort Network (NAPKON) of the Network University Medicine (NUM; Schons et al., 2022). Participants were recruited in catchment areas around Kiel (Northern Germany), Würzburg (Southern Germany), and in the Neukölln district of Berlin (Eastern Germany). Inclusion criteria were a positive polymerase chain reaction (PCR) test for SARS-CoV-2, a period of at least 6 months between the infection and the baseline visit to the COVIDOM study site, and age ≥ 18 years at the time of infection. Exclusion criterion was an acute reinfection with SARS-CoV-2 at the time of the scheduled study visit. Details on design, methods and overall sample size calculation are provided in the study protocol (Horn et al., 2021). The criterion for including data in our analysis were the availability of the Patient Health Questionnaire (PHQ-8) scores for depression (Kroenke et al., 2009) and the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scores (Vogelzang et al., 1997). All data were collected between November 15, 2020 and January 22, 2023.

2.2. Data preprocessing

We selected 103 items on the basis of expert knowledge and literature research. We then excluded 51 survey items that had >20 % missing data across all study sites. For the remaining 52 items, we applied an iterative imputation method based on a random forest using the "missForest" package in *R* (R Core Team, 2021) to obtain a data set without missing values (Stekhoven and Bühlmann, 2012). A list of all included items can be found in Table S1 in the Supplementary Materials.

In order to accurately classify clinically relevant levels of depression, we generated a binary target variable (1 = depressed, 0 = non-depressed) using the established cutoff of ≥10 in the PHQ-8 (Kroenke et al., 2009). For fatigue, we also generated a binary target variable (1 = fatigue, 0 = no fatigue) based on the cutoff of ≤34 in the FACIT-F score (Vogelzang et al., 1997). To classify imbalanced data accurately, we used the synthetic minority oversampling technique (SMOTE) for the

minority classes of depression and fatigue (Chawla et al., 2002). SMOTE generates synthetic instances rather than replicating minority class instances, thereby reducing bias towards the majority without increasing the risk of over-fitting.

2.3. Final set of variables

We included 50 variables into the models, such as sociodemographic information (age, sex, education, partner), COVID-related information (recovery, received treatment, risk group), variables associated to post-COVID syndrome severity (impaired concentration, sleep disturbance, vertigo, shortness of breath, muscle or joint pain, flu-like symptoms), information regarding previous depression or anxiety disorders, questionnaires (perceived stress, social and emotional loneliness, *Montreal-Cognitive-Assessment-Test-scores*, Canadian Criteria for chronic fatigue syndrome, health-related quality of life [QOL]), and items assessing social aspects (problems [5 items], job-related changes [6 items]), respiratory and neurological symptoms (e.g., thought disorder, mental and bodily fatigue [13 items]; see Table S1).

2.4. Statistical analyses

First, we used elastic net logistic regression, a regularized regression method, to classify cases with symptoms of depression and fatigue with two separate models. Elastic net regression addresses multicollinearity between the regressors and enables selecting the most informative ones. The algorithm regularizes (i.e., shrinks) the estimated β coefficients by applying a penalization based on two hyperparameters. The first hyperparameter is α - an indicator of the type of penalty - ranging from a ridge penalty when α approaches 0 to a lasso penalty when α approaches 1. The second hyperparameter is λ, which identifies the amount of penalization (λ = 0 means no shrinkage is performed and increasing λ means the coefficients are shrunk ever more strongly; Zou and Hastie, 2005) Previous research showed that elastic net logistic regression results in similar model performance to random forest and XGBoost in predicting depression and anxiety during the COVID-19 pandemic, and was the preferred algorithm because of its effectiveness, interpretability, and simplicity (Simjanoski et al., 2022).

First, we applied 10-fold repeated cross-validation to train and tune our models over a grid of α and λ hyperparameters on 80 % of the sample, i.e., the training data set. Second, we refitted the models on the training data set with the best performing hyperparameters to calculate the final penalized β coefficients. Third, we applied the models to the remaining 20 % of the sample, i.e., the testing data set, to estimate model performance (accuracy, area under the receiver operating characteristic curve [AUROC], sensitivity, specificity, positive and negative predictive value, balanced accuracy, and Cohen's kappa). Using the R package *caret* (Kuhn, 2008), we conducted AUROC analyses separately for the depression and the fatigue model to calculate the importance of each variable (for all AUROC importance values, see Table S1). A higher AUROC value (range from 0 to 1) indicates better performance of the classifier and is therefore an indication of high variable importance. We correlated the resulting model-specific importance scores of both models to investigate the potential overlap of symptom constellations. To help interpreting the direction of the associations, we included the five variables with the highest importance scores (top 10 %) in a simpler logistic regression model for depression and fatigue. For the external validation of the results, we used two data sets from other sites (i.e., Berlin and Würzburg) that contained the same variables as the training data set from Kiel. This approach allowed for testing, whether the prediction model obtained from the training data set was reproducible and generalizable.

Once the top five variables for each target variable were identified, we combined them to create a new data set containing the five most important variables related to each outcome variable, depression and fatigue. We standardized all values of the new data set in a manner that they ranged from 0 to 1. This new data set was then used to perform a hierarchical cluster analysis using gower distance and average linkage. The resulting clusters were then interpreted to further analyze differences and overlaps in symptom constellations of post-COVID depression and fatigue.

3. Results

3.1. Sample characteristics

We retrieved 2247 data sets from University Medical Center Schleswig-Holstein, Campus Kiel. 7.5 % had missing values in at least one of the dependent variables and were excluded. Thus, we used data of 2079 participants (57.7 % female, median age = 45, age range 18–87) for our main analyses. To validate the performance of our models, we used data from the University Hospital Charité in Berlin (n = 398) and the University Hospital Würzburg (n = 484). After excluding data sets with missing values in the depression and/or the fatigue score, n = 375 (Berlin) and n = 479 (Würzburg) were included in the validation sets (see Fig. 1). The prevalence of self-reported depression was 19.7 % in the Kiel sub-cohort, whereas in the Berlin and Würzburg sub-cohorts the prevalence was lower, i.e., 13.9 % and 10.4 %, respectively. Self-reported fatigue prevalence was also higher in the Kiel cohort (22.8 %) than in the other cohorts (Berlin 15.7 %, Würzburg 11.1 %). For an overview of prevalence and sample characteristics for each sub-cohort, see Table 1.

3.2. Depression

The classification model for depression had an overall accuracy of 86.3 % with a 95 %-confidence interval of [82.6 %, 89.5 %] and an AUROC of 0.900. The accuracy was significantly better than the no information rate (NIR 80.5 %, p = .001). It performed well in classifying healthy participants (specificity 97.0 %) but showed a mediocre sensitivity of 42.0 %. Despite that, it was able to classify individuals with depression scores above cut-off (positive predictive value 77.3 %) and healthy participants (negative predictive value 87.4 %). Overall, the model had a kappa value of 0.472 and a balanced accuracy of 69.5 %.

The external validation of this elastic net model was conducted using two independent data sets from the Berlin (n = 375) and the Würzburg (n = 479) site. The achieved accuracies were similar to the test accuracy (89.1 % for Berlin data and 92.3 % for Würzburg data; see Table 2 for further performance scores of all validation data sets). These results demonstrated the robustness of the elastic net model in predicting depression across different populations and locations within Germany.

The top five variables associated with the classification of depression were *problems with daily activities*, *health-related QOL*, *unrestful sleep*, *impaired concentration,* and *chronic exhaustion* (Fig. 2, upper panel). A logistic regression with these five independent variables and depression scores as dependent variable was significant. (χ^2 643.0, p < .001, Nagelkerke R^2 0.517). It showed that all independent variables were significantly associated with the odds of having depressive symptoms, with the exception of *chronic exhaustion* (see Table 3).

3.3. Fatigue

The classification model for fatigue showed an overall accuracy of 80.8 % with a 95 % confidence interval of [76.7 %, 84.5 %] and an AUROC of 0.895. The difference in information rate compared to the no information rate was significant (NIR 77.2 %, p = .043). The model had a sensitivity of 80.0 % and a specificity of 81.0 %. It successfully classified between healthy individuals and individuals with fatigue (negative predictive value 93.2 %; positive predictive value 55.5 % indicating a higher false positive rate than false negative rate). Overall, the model had a moderate performance, as indicated by its kappa value of 0.528 and its balanced accuracy of 80.5 %.

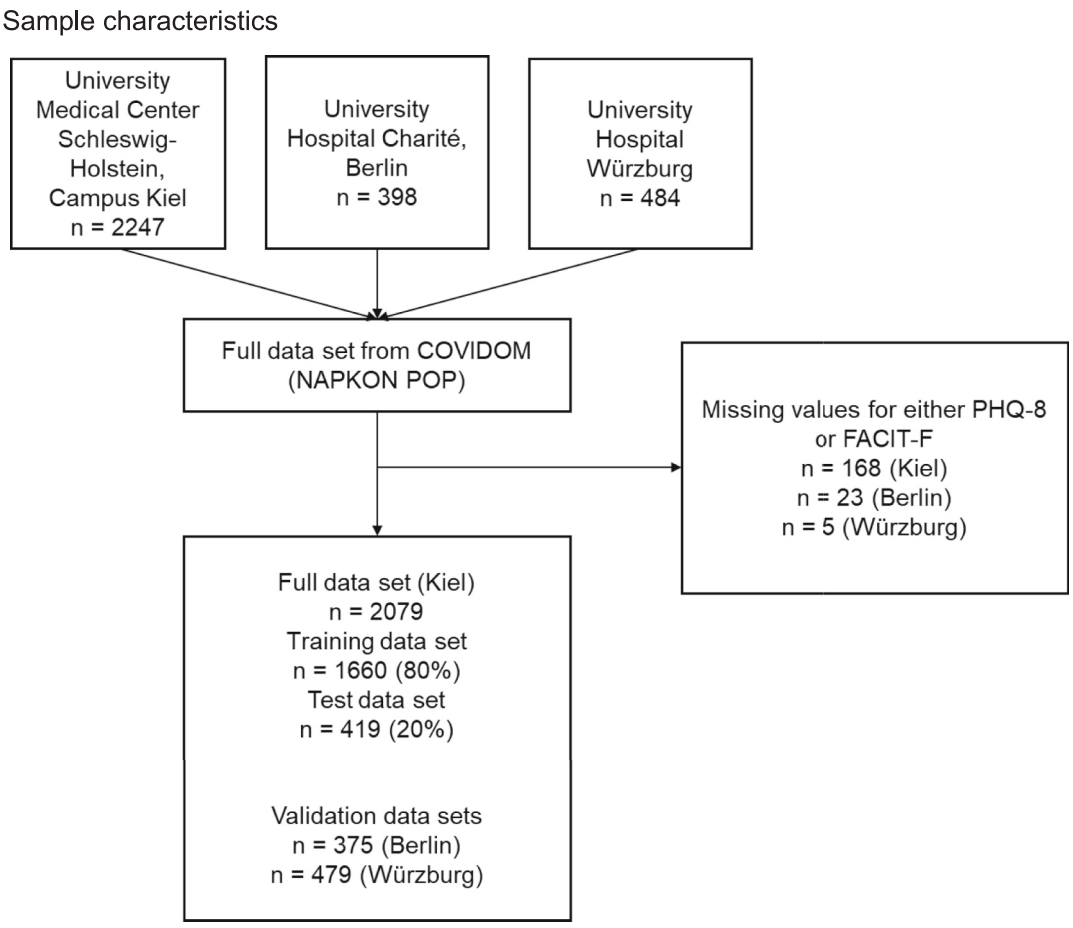

Fig. 1. Data retrieval and exclusion flowchart.

Table 1
Prevalence of self-reported depression (PHQ-8) and fatigue (FACIT-F) and sample characteristics for each location where data was collected.

	Kiel ***n*** = 2079 n (%)	Berlin ***n*** = 375 n (%)	Würzburg ***n*** = 479 n (%)
PHQ-8 ≥ 10	410 (19.7 %)	52 (13.9 %)	50 (10.4 %)
FACIT-F ≤ 34	474 (22.8 %)	59 (15.7 %)	53 (11.1 %)
Sex			
Female / Male	1200 / 879	196 / 179	254 / 225
Percent female	57.7 %	52.3 %	53.0 %
Age			
Range	18–87	19–85	19–86
Median (SD)	45 (15.1)	38 (14.2)	45 (16.7)

Table 2
Performance measures for the depression elastic net model over three validation sets.

Performance parameter	Kiel (test set) *n* = 419	Berlin *n* = 377	Würzburg n = 479
Accuracy	0.863	0.891	0.923
[95 % CI]	[0.826, 0.895]	[0.855, 0.920]	[0.895, 0.945]
p [Acc > NIR]	0.001	0.054	0.027
Sensitivity	0.420	0.346	0.440
Specificity	0.970	0.978	0.979
Positive predictive value	0.773	0.720	0.710
Negative predictive value	0.874	0.903	0.938
Balanced accuracy	0.695	0.662	0.710
AUROC	0.900	0.899	0.891
Kappa	0.472	0.415	0.504

Note. CI = confidence interval, NIR = No-information rate, AUROC = area under the receiver operating characteristic.

Similar to the depression model, the external validation of the elastic net model for fatigue proved the robustness of the model across different populations, indicated by accuracies that ranged from 79.2 % (Berlin) to 83.9 % (Würzburg); see Table 4 for further performance scores of all validation data set.

The top five variables associated with the classification of fatigue were identical to the classification of depression: *Problems with daily activities* was the most important variable (as in the depression model), followed by *chronic exhaustion, health-related QOL, unrestful sleep,* and *impaired concentration* (Fig. 2, lower panel). The logistic regression with fatigue as dependent variable and those five independent variables was significant (χ^2 792.83, $p < .001$, Nagelkerke R^2 0.571). It showed that all independent variables were significantly associated with the odds of suffering from symptoms of fatigue. All coefficients can be seen in Table 5.

3.4. Overlapping symptom constellations

Both target variables depression and fatigue have a moderate to high Pearson correlation ($r = 0.66$, $p < .001$) in the Kiel data set. To investigate if associated variables for both models differ or also tend to overlap, we calculated the Pearson correlation between AUROC as an importance measure of all variables in both models. This yielded a high positive correlation of $r = 0.98$ ($p < .001$), indicating a strong overlap of the symptom constellations and the variable importance for each model.

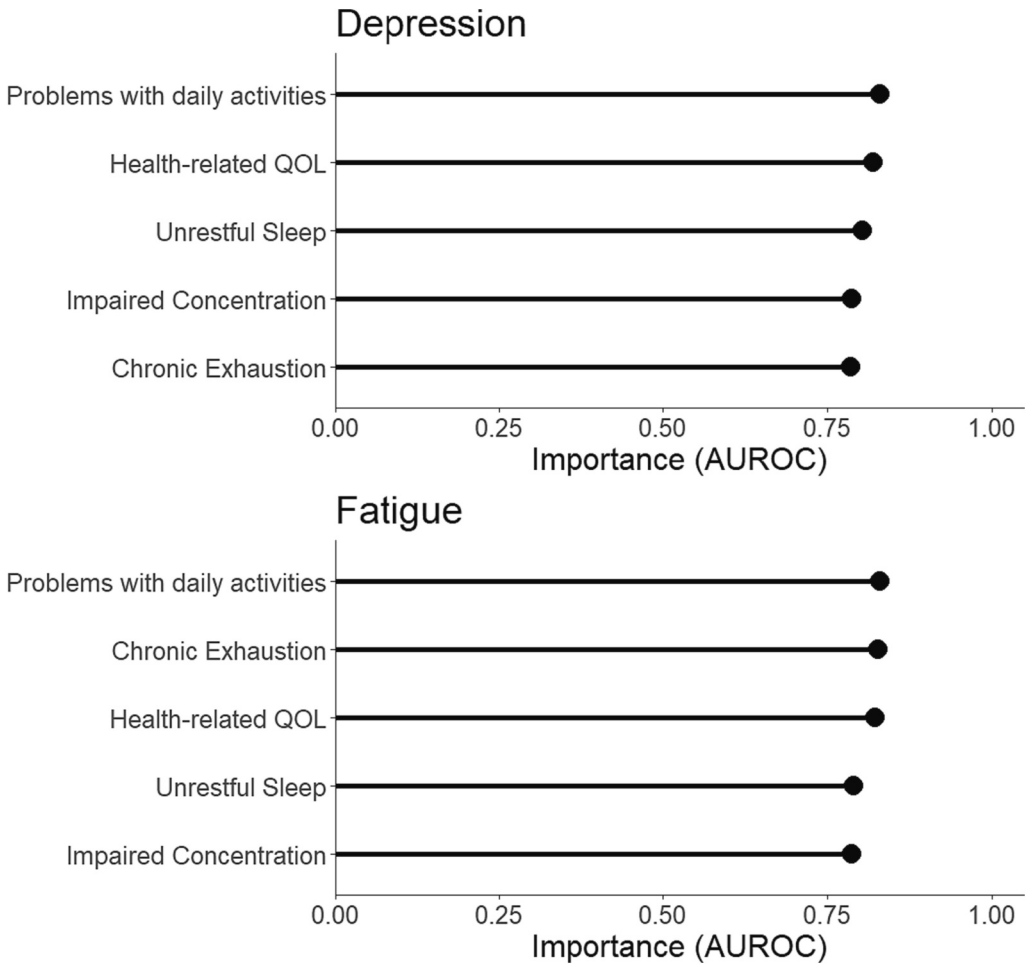

Fig. 2. The five most relevant variables for the classification of depression (upper panel) and fatigue (lower panel) ordered by their AUROC importance.

Table 3
Coefficients and Odds-Ratios of the logistic regression on depression with top 5 variables of the elastic net regression.

Independent variable	Estimate	SE	z	p	OR [95%CI]
(Intercept)	−2.02	0.09	−22.87	<0.001	0.13 [0.11, 0.16]
Problems with daily activities	0.40	0.09	4.40	<0.001	1.48 [1.25, 1.77]
Health-related QOL	−0.61	0.09	−7.14	<0.001	0.54 [0.46, 0.64]
Unrestful Sleep	0.47	0.08	5.81	<0.001	1.60 [1.36, 1.87]
Impaired Concentration	0.43	0.09	4.61	<0.001	1.53 [1.28, 1.84]
Chronic Exhaustion	0.13	0.11	1.24	0.214	1.14 [0.93, 1.40]

Note. SE = standard error of the mean, OR = odd's ratio, CI = confidence interval.

3.5. Cluster analysis

The results of the hierarchical cluster analysis showed that the data could be grouped into two clusters (based on total within sum of square, see Fig. 3, Panel A; see Fig. S2 for elbow plot). These clusters were characterized by the following traits: Cluster 1 (n = 1605) contains individuals with low depression rates and no fatigue, fewer problems with daily activities, higher health-related QOL, less chronic exhaustion, less unrestful sleep, and less impaired concentration. In sum, cluster 1 consists of healthy individuals. Cluster 2 (n = 474), in contrast, contains individuals with high depression and fatigue rates, more problems with daily activities, lower health-related quality of life, higher rates of chronic exhaustion, unrestful sleep and impaired concentration. Thus, cluster 2 consisted of individuals suffering from both fatigue and depression (see Fig. 3, Panel B). Importantly, the cluster analysis could

Table 4
Performance measures for the fatigue elastic net model over three validation sets.

Performance parameter	Kiel (test set) n = 419	Berlin n = 377	Würzburg n = 480
Accuracy [95 % CI]	0.808 [0.767, 0.845]	0.792 [0.747, 0.832]	0.839 [0.803, 0.871]
p [Acc > NIR]	0.043	0.996	0.999
Sensitivity	0.800	0.695	0.727
Specificity	0.810	0.810	0.854
Positive predictive value	0.555	0.406	0.380
Negative predictive value	0.932	0.934	0.960
Balanced accuracy	0.805	0.753	0.786
AUROC	0.895	0.832	0.882
Kappa	0.528	0.392	0.412

Note. CI = confidence interval, NIR = No-information rate, AUROC = area under the receiver operating characteristic.

Table 5
Coefficients and Odds-Ratios of the logistic regression on fatigue with top 5 variables of the elastic net regression.

Independent variable	Estimate	SE	z	p	OR [95%CI]
(Intercept)	−1.87	0.09	−21.31	<0.001	0.15 [0.13,0.18]
Problems with daily activities	0.36	0.09	4.06	<0.001	1.44 [1.21,1.72]
Chronic exhaustion	0.66	0.10	6.41	<0.001	1.94 [1.59,2.38]
Health-related QOL	−0.55	0.09	−6.33	<0.001	0.58 [0.49,0.69]
Unrestful sleep	0.40	0.08	5.00	<0.001	1.49 [1.27,1.74]
Impaired concentration	0.33	0.09	3.58	<0.001	1.39 [1.16,1.66]

Note. SE = standard error of the mean, OR = odd's ratio, CI = confidence interval.

not differentiate between patients with depression and patients with fatigue, confirming the overlap in symptom constellations observed above.

4. Discussion

We analyzed data from a population-based, prospective multi-centre study to identify and compare symptom constellations of post-COVID depression and fatigue. As a main result, elastic net regressions revealed a strong overlap in variables associated with the development of symptoms of depression and fatigue six month after a SARS-CoV-2 infection. Importantly, these results were replicated with two independent data sets that were collected in different regions of Germany. While the prevalence of self-reported depression and fatigue in the training data set were comparable to previous studies (Mazza et al., 2022), the prevalence rates in the replication data sets were sizably lower (see Table 1). Despite of these differences, the results of the initial depression and fatigue models were fully replicated in the data sets from the two other sites, indicating strong model robustness and generalizability. Further validating the overlap in symptom constellations of post-COVID depression and fatigue, a cluster analysis showed that patients with high levels of post-COVID depression and fatigue symptoms form one cluster.

In more detail, we found that the most important variables associated with both post-COVID depression and post-COVID fatigue were problems with daily activities, low perceived health-related QOL, chronic exhaustion, and two symptoms related to post-COVID syndrome severity: unrestful sleep, and impaired concentration. Previous studies showed that specificities such as female sex, a history of psychiatric symptoms, or specifics of the course of the COVID disease are common risk factors for post-COVID depression and fatigue (for reviews and perspectives, see Renaud-Charest et al., 2021; Rudroff et al., 2020; Joli et al., 2022). Moreover, the overview by Ceban et al. (2022) showed that functional impairment of QOL post-COVID was reported by 21 % to 63 % of those affected. Extending this previous work, our studies focused on the differences in symptom constellations between post-COVID depression and fatigue. We observed a striking overlap in symptom constellations between post-COVID depression and fatigue, although we used large set of variables that maximized the probability to detect differences. Thus, our findings provide strong support for the claim that post-

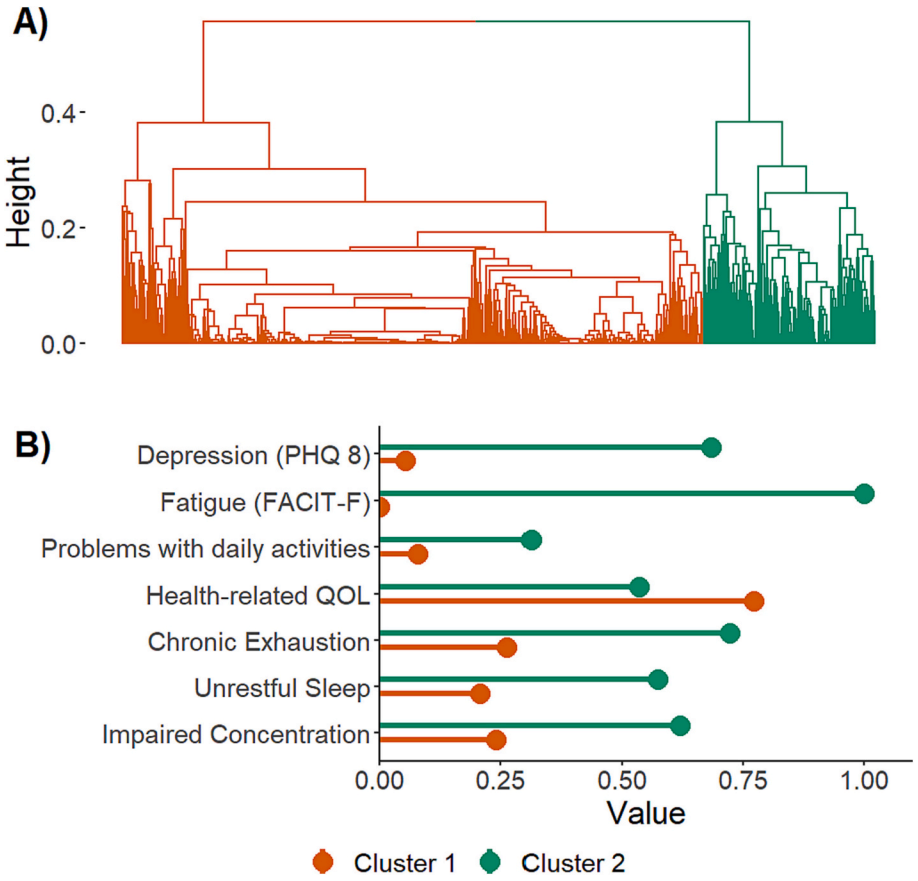

Fig. 3. (A) Cluster dendrogram depicting the results of the cluster analysis based on the combined standardized top five variables associated with the depression and the fatigue model as well as depression and fatigue scores. (B) Mean values and rates of outcome variables and top five associated variables for each cluster. Orange: cluster 1 (n = 1605); green: cluster 2 (n = 474). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

COVID depression and fatigue might be linked and often occur in concert.

The observed overlap in symptom constellations is in line with a previous study showing that the severity of the post-COVID syndrome (ascertained by the occurrence of specific long term symptoms) was related to both post-COVID depression and fatigue (Bahmer et al., 2022). Our study showed that the occurrence of symptom constellations associated with the severity of post-COVID syndrome (see Table S1) was strongly related to *both* post-COVID depression and fatigue but did not contribute to a differentiation between those two syndromes. These results confirm the importance of the severity of symptoms as general predictors for post-COVID sequelae (Bahmer et al., 2022). Supporting this evidence, variables reflecting respiratory impairments (e.g., shortness of breath) and the severity of the disease progression (approximated by treatment intensity and disease duration) were not among the variables most strongly related to fatigue and where thus also not able to distinguish it from post-COVID depression (see Table S1). Extending these findings, previous research has also investigated the relationship between depression and fatigue in patients with multiple sclerosis, another disease often associated with both syndromes. Using self-report questionnaires and a full night polysomnography (i.e., electroencephalography, electromyogram, electrocardiogram, etc.) followed by the maintenance of wakefulness test the following day, the authors were also not able to differentiate depression from fatigue in this patient group, again supporting the overlap and strong associations between both syndromes (Sparasci et al., 2022).

The similarities of symptom constellations described above were also confirmed in external validations and a cluster analysis. However, it is important to note that the data utilized predominantly came from self-reported questionnaire or anamnesis, rather than biometric recordings. Future studies should test whether the overlap of depression and fatigue is maintained if neurobiological and -endocrine markers, for example abnormal hypothalamic-pituitary-adrenal axis activity, are included (Iob et al., 2020), and assess depression and fatigue in more detail, instead of solely relying on self-reports. Moreover, the results of our cross-sectional study that revealed variables that are strongly associated with depression and fatigue can inspire future longitudinal studies that can further specify the observed effects.

The current finding of overlapping symptom constellations is of clinical importance because it indicates that patients with post-COVID fatigue might benefit from depression treatment and, vice versa, patients diagnosed with post-COVID depression might benefit from treatments targeting fatigue symptoms. In more detail, our results have implications for short-, medium-, and long-term actions that practitioners and health agencies should put in place. Regarding short-term actions, we suggest that COVID patients should be seen by interdisciplinary medical teams who are able to diagnose depression and fatigue properly, and to coordinate respective treatment options. Patients with increased risk for depression should be offered additional therapeutic and, if necessary, psychopharmacological, support when infected with COVID-19, because they are also more likely to experience a worsening of symptoms due to fatigue. There is evidence that early treatment with selective serotonin reuptake inhibitors can have beneficial effects on the course of the COVID-19 infection and could mitigate the course of the disease preventively (Lenze et al., 2020; Mazza et al., 2022; Reis et al., 2022). Given a successful evaluation in further studies, such medication may enter the guidelines for the treatment of post-COVID in certain risk groups. Along the same lines, there is meta-analytical evidence suggesting that patients with tumor-associated fatigue benefit from treatment with stimulants and antidepressants (Tomlinson et al., 2018; Hellwig and Domschke, 2022). Also, other treatment methods, for example cognitive behavioral therapy seem to have an effect on both chronic depression (Hofmann et al., 2012) as well as chronic fatigue, especially in the presence of comorbid depression (Castell et al., 2011). For example, patients could benefit greatly from increased physical activity to reduce symptoms of post-COVID fatigue (Coscia et al., 2023) and simultaneously symptoms of depression (Dinas et al., 2011). This could be a way to make use of synergies in the treatment of both syndromes.

As a mid-term action, we recommend that the respective interdisciplinary teams should be encouraged and financed to develop new integrative treatment approaches that are implemented in new clinical guidelines, for example in planned post-COVID clinics. For instance, there is work on post-COVID guidelines with the parallel effort to create a multidisciplinary post-COVID clinic (Vance et al., 2021). Setting up the guidelines, the authors collaborated within their local hospital system, which included primary care, occupational health service, infectious disease, physical medicine and rehabilitation, highlighting the interdisciplinary effort. As a result, the authors propose a quick-reference guide for the management of post-COVID symptoms, outlining the outpatient evaluation and treatment for post-COVID symptoms.

With regard to long-term actions, our findings imply that political and societal measures (for example taken to control pandemics in the future), should strive to minimize risk factors for depression, as it is paralleled by other impairments such as fatigue. Health care agencies should possess the necessary workforce and financial resources to approach persons with high risk of depression and to offer tailored support inside and outside of clinical settings, in times of crises and beyond. Persons that are at risk for both depression and post-COVID fatigue include females (depression: Albert, 2015; fatigue: Asadi-Pooya et al., 2021), individuals experiencing stress and/or loneliness (depression: Mushtaq et al., 2014; fatigue: Wang et al., 2022), or hospitalized patients (depression: Fernández-de-las-Peñas et al., 2021; fatigue: Iqbal et al., 2021). These groups of individuals should be approached with prevention programs that, for example, encourage physical activities (Luo et al., 2022) or daily communication with close persons (Takada et al., 2022) to mitigate the risk of fatigue and depression.

To date, the development of guidelines for the treatment of post-COVID fatigue and depression is an ongoing and much debated process. Approaches combining aspects of traditional depression and fatigue treatments are discussed (Kuut et al., 2021), but are not yet implemented in recommendations. The current report provides externally validated evidence that depressive and fatigue symptoms occurring after a SARS-CoV-2 infection overlap regarding symptom constellations. These findings thus support the necessity of integrative treatment approaches in patients with established post-COVID depression and post-COVID fatigue.

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CRediT authorship contribution statement

Martin Weiß: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Julian Gutzeit:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Katharina S. Appel:** Writing – review & editing. **Thomas Bahmer:** Funding acquisition, Investigation, Project administration, Writing – review & editing. **Manfred Beutel:** Writing – review & editing. **Jürgen Deckert:** Writing – review & editing. **Julia Fricke:** Conceptualization, Writing – review & editing. **Sabine Hanß:** Writing – review & editing.

Nora Hettich-Damm: Writing – review & editing. **Peter U. Heuschmann:** Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Anna Horn:** Writing – review & editing. **Kamila Jauch-Chara:** Conceptualization, Writing – review & editing. **Mirjam Kohls:** Writing – review & editing. **Lilian Krist:** Writing – review & editing. **Bettina Lorenz-Depiereux:** Writing – review & editing. **Christian Otte:** Writing – review & editing. **Daniel Pape:** Writing – review & editing. **Jens-Peter Reese:** Writing – review & editing. **Stefan Schreiber:** Writing – review & editing. **Stefan Störk:** Funding acquisition, Project administration, Writing – review & editing. **Jörg Janne Vehreschild:** Writing – review & editing. **Grit Hein:** Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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