Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Affective Disorders 338 (2023) 384–392

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Anxiety and depression played a central role in the COVID-19 mental distress: A network analysis

Giovanna Fico [a,b,c,d], Vincenzo Oliva [b,f], Michele De Prisco [b,e,g], Lydia Fortea [a,c,h], Adriana Fortea [a,c,e], Anna Giménez-Palomo [b,c], Gerard Anmella [a,b,c,d], Diego Hidalgo-Mazzei [a,b,c,d], Mireia Vazquez [a,e], Marta Gomez-Ramiro [a,c,e,n], Bernat Carreras [b], Andrea Murru [a,b,c,d,e], Joaquim Radua [e,h,i,j], Philippe Mortier [k,l], Gemma Vilagut [k,l], Franco Amigo [k,l], Montse Ferrer [k,l,m], Helena García-Mieres [l,m], Eduard Vieta [a,b,c,d,e,*], Jordi Alonso [k,l,m]

[a] Departament de Medicina, Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona (UB), c. Casanova, 143, 08036 Barcelona, Spain
[b] Bipolar and Depressive Disorders Unit, Hospital Clinic de Barcelona, c. Villarroel, 170, 08036 Barcelona, Spain
[c] Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), c. Villarroel, 170, 08036 Barcelona, Spain
[d] Institute of Neurosciences (UBNeuro), p. de la Vall d'Hebron, 171, 08035 Barcelona, Spain
[e] CIBER de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain
[f] Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy
[g] Section of Psychiatry, Department of Neuroscience, Reproductive Science and Odontostomatology, Federico II University of Naples, Naples, Italy
[h] Imaging of Mood- and Anxiety-Related Disorders (IMARD) Group, IDIBAPS, Barcelona, Spain
[i] Early Psychosis: Interventions and Clinical-Detection (EPIC) Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom
[j] Centre for Psychiatric Research and Education, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[k] Health Services Research Unit, IMIM-Institut Hospital del Mar d'Investigacions Mèdiques, Barcelona, Spain
[l] CIBER Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III, Spain
[m] Dept. Medicine and Life Sciences, Universitat Pompeu Fabra (UPF), Barcelona, Spain
[n] Hospital Alvaro Cunqueiro, SERGAS, Translational Neuroscience Research Group, Galicia Sur Health Research Institute (IISGS), Vigo, Spain

ARTICLE INFO

Keywords:
COVID-19
Mental health
Depressive disorder
Social support
PTSD
Resilience
Hospitalization
Lockdown
Network analysis

ABSTRACT

Introduction: Psychological, socio-demographics, and clinical factors play an important role in patients with COVID-19, but their relationship is complex. The network approach might be used to disentangle complex interactions in different systems. Using data from a multicentre, cross-sectional, survey among patients with COVID-19 in Spain (July–November 2020), we investigated the network structure of mental disorders symptoms, social support, and psychological resilience, and changes in network structures according to the presence of a pre-existing mental disorder or hospitalization for COVID-19.

Methods: Subjects completed a survey to evaluate sociodemographic characteristics, COVID-19 infection status, resilience, social support, and symptoms of depression, anxiety disorders, post-traumatic stress disorder, panic attacks, and substance use disorder. 2084 patients with COVID-19 were included in the analysis. Network analysis was conducted to evaluate network and bridge centrality, and the network properties were compared between COVID-19 patients with and without a history of lifetime mental disorder, and between hospitalized and non-hospitalized patients.

Limitations: Generalization of our findings may be difficult since differences in network connectivity may exist in different populations or samples.

Results: Anxiety and depression showed high centrality in patients with COVID-19 and anxiety showed the highest bridge influence in the network. Resilience and social support showed a low influence on mental disorder symptoms. Global network estimations show no statistically significant changes between patients with and without pre-existing mental disorders or between hospitalized and non-hospitalized patients.

* Corresponding author at: Bipolar and Depressive Disorders Unit, IDIBAPS CIBERSAM, Hospital Clinic, University of Barcelona, 170 Villarroel St, 08036 Barcelona, Catalonia, Spain.
E-mail address: evieta@clinic.cat (E. Vieta).

https://doi.org/10.1016/j.jad.2023.06.034
Received 23 December 2022; Received in revised form 12 June 2023; Accepted 16 June 2023
Available online 17 June 2023

Conclusions: Anxiety might be a key treatment target in patients with COVID-19 since its treatment might prevent other mental health adverse outcomes.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a serious viral upper respiratory infection with a broad spectrum of clinical manifestations, including neurologic and neuropsychiatric symptoms (Torous and Keshavan, 2020). As the number of infections and COVID-19-related deaths increased (Pacchiarotti et al., 2020), many patients experienced physical problems and psychological distress. Indeed, a high prevalence of anxiety, depression, and stress-related symptoms has been widely reported among patients with COVID-19, ranging from 30 % to 50 % (Taquet et al., 2021),and hospital workers (Gómez-Ramiro et al., 2021; Mortier et al., 2022), calculated to be up to 50 % in the most affected countries (Lai et al., 2020).

The impact of the pandemic on mental health quickly became evident worldwide in the first wave, due also to the imposition of social restrictions to avoid COVID-19 spread. Long-term negative mental health consequences, however, were also reported as a result of the pandemic, with a global increase in depression and anxiety prevalence (Santomauro et al., 2021), increase of substance abuse (Pirkis et al., 2021), suicidal behavior among adults and adolescents (Charpignon et al., 2022), and clinical worsening of patients with pre-existing mental disorders, imposing new challenges on mental health professionals (Solé et al., 2021; Taquet et al., 2021). Potential protective factors against mental health distress, such as social support or resilience, have been proposed as potential targets of intervention in special populations at risk of severe psychological outcomes (Li et al., 2021; Verdolini et al., 2021).

Patients with pre-existing psychiatric disorders are considered a fragile population, with a higher risk of COVID-19 infection and mortality (de Hert et al., 2022; Nemani et al., 2021). In addition, they may have an impaired ability to access medical care due to stigma, cognitive deficits, or poor insight, thus resulting in worse global outcomes after COVID-19 infection (Vai et al., 2021; Vieta et al., 2020a).

However, patients hospitalized for COVID-19 may also be subject to worse mental health (Epstein et al., 2020) or cognitive outcomes (Llach and Anmella, 2022; Miskowiak et al., 2022), since they may have several physical complications after hospital discharge and being exposed to various external stressors, such as isolation, economic problems, or lack of social support (Matalon et al., 2021) or internal, biologically related factors (Fico et al., 2022). Furthermore, hospitalization for COVID-19 might worsen previous psychiatric symptoms or conditions, and treatment for COVID-19 may have adverse effects on mental health and contribute to problems such as anxiety and insomnia (Zhou et al., 2020). Patients with COVID-19 have been found to be at higher risk of experiencing severe mental health problems, such as delirium and psychosis, also compared to their close contacts (Rogers et al., 2020).

The COVID-19 pandemic represents an unprecedented example of how psychiatric symptoms and more direct infection-related symptoms may generate complex interactions, being influenced by the course of infection, personal physical and psychological aspects, and external factors. The network approach, in this perspective, may be particularly useful for analyzing and visualizing complex relationships among psychopathology symptoms in specific populations (Borsboom and Cramer, 2013). By applying network analysis to psychiatric symptoms, researchers can gain insights into the complex interactions between them and identify key symptoms that may play a central role in the development and maintenance of a disorder. In network analysis, nodes reflect symptoms, and edges between nodes reflect relationships between symptoms. Some common concepts and techniques used in network analysis include centrality measures, which identify the most important nodes in a network; clustering algorithms, which group nodes based on their structural similarities; and community detection algorithms, which identify groups of nodes that are densely connected to each other. Also, in network theory, central symptoms are more likely to activate other symptoms and may play a major role in mental disorders onset or maintenance thus providing hints for clinicians to target specific aspects of a complex phenomenon (Borsboom et al., 2021). By understanding these relationships, healthcare providers can develop more effective treatment plans for patients with COVID-19. Additionally, network analysis can help researchers identify potential new targets for intervention, such as specific symptoms or risk factors that are strongly associated with poor mental health outcomes. Overall, network analysis can provide a powerful tool for understanding the complex interplay between physical and mental health in patients with COVID-19 (Borsboom et al., 2021).

In the current study, we aimed to investigate the network structure of depressive, anxiety, and post-traumatic symptoms as well as the resilience strategies and social support in a large, multicentric, Spanish sample of patients with COVID-19 infection. Specifically, we aimed to examine how psychiatric symptoms and coping strategies are related in patients with COVID-19. Secondarily, we aimed to analyze possible differences between the network structures of patients with and without a history of psychiatric illness, as well as those with and without hospitalization for COVID-19.

2. Methods

2.1. Participants

We analyzed data from a cross-sectional survey conducted in a representative sample of COVID-19 patients as part of the MIND/COVID project. The target population consisted of COVID-19 patients and close contacts aged 18 years or older from 10 different health institutions from 5 autonomous communities in Spain (Basque Country, Castilla y León, Catalonia, Madrid, and Valencia). The institutions were selected to reflect the geographic and sociodemographic variability in Spain; most of the participating centers came from regions with a high number of COVID-19 cases. A baseline evaluation and two follow-up evaluations have been carried out through the institutional email of the participants, using the Qualtrics(R) platform, and through telephone interviews, using the GESOP platform. Each of the participating centers carried out its own recruitment of cases and/or close contacts of COVID-19. The sample frame was obtained from information from the different local and regional epidemiological services, and from the different health services (hospitals and primary care centers) in charge of identifying and managing COVID-19 patients and their close contacts. Recruitment was carried out both in person and by telephone: for those people recruited in person, a visit to the health center or discharge was used to inform them about the study and invite them to participate, while for those who were invited by telephone, this was done retrospectively, using the available contact information. The baseline assessment consisted of anonymous self-reported surveys via the web (qualtrics.com) or by computer-assisted telephone interviews (CATI), conducted by a specialized company or by people hired at the centers. The centers invited 6604 people to participate.

5194 people accepted to participate in the study, and 2619 people finally participated. Filtering by response quality criteria, we were left with 2504 patients/cases. Of those, 2084 were COVID cases (Flowchart - Supplementary Material). Ethical approval was provided by the Parc de Salut Mar Clinical Research Ethics Committee (protocol 2020/9203/I).

Participants were fully informed about the objectives and procedures of the study prior to providing consent.

2.2. Variables assessment

2.2.1. Sociodemographic and clinical measures

Sociodemographic variables included age, gender, marital status, income, financial problems, educational level, and living situation. Medical comorbidities were recollected using a checklist of conditions considered as vulnerable to COVID-19. Clinical data on COVID-19 infection included: infection (Y/N), and hospitalization in a COVID-19 facility or intensive care unit (ICU).

2.2.2. Mental health measures

Pre-pandemic lifetime mental disorders were assessed using a checklist based on the Composite International Diagnostic Interview (CIDI) (Kessler and Üstün, 2004), that screen the presence of depressive disorder, bipolar disorder, generalized anxiety disorder (GAD), panic disorder (PD), alcohol and drug use disorders, and "other" mental disorders. A dichotomous variable (Y/N) was created (participants with ≥ 1 pre-pandemic mental disorder, vs. none).

Depressive symptoms of the previous two weeks were measured with the eight-item Patient Health Questionnaire depression scale (PHQ-8) (Kroenke et al., 2009), which reflects eight of the nine criteria on which DSM-5 diagnosis of major depressive disorder is based and which scores range from 0 to 24 (Wu et al., 2020). The PHQ-8 omits the item of the PHQ-9 regarding suicidal ideation and self-harm and performs similarly to the PHQ-9 in terms of diagnostic accuracy (Wu et al., 2020). Therefore, also in our study, the cut-off point of 10 was used to indicate a positive screen for current major depressive disorder (Wu et al., 2020). Generalized anxiety symptoms during the previous two weeks were measured with the Generalized Anxiety Disorder Scale (GAD-7) (Spitzer et al., 2006), which scores range from 0 to 21 and is a validated and reliable instrument used in different populations, including the general population during COVID-19 pandemic (Shevlin et al., 2022) PTSD symptoms during the previous 30 days were measured by means of four items of the PTSD Checklist for the DSM-5 (PCL-5) (Bovin et al., 2016), which scores range from 0 to 16 (Zuromski et al., 2019). The presence of substance use disorder was assessed with the CAGE-AID (Leonardson et al., 2005; Moore et al., 2002) questionnaire, which has high reported validity in different samples (Mdege and Lang, 2011) with a score of two points set as a cut-off to indicate current SUD. All higher scores from previously mentioned scales indicate more severe symptomatology. Having had any suicidal ideation or behavior in the previous 30 days was assessed by a modified version of selected items from the Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011). All responses to the five dichotomous questions of the scale were combined, and a general dichotomous variable (suicidal thoughts and behaviours [STB]) was created to measure if any of the questions were answered with a "yes".

2.2.3. Resilience and social support measures

Resilience was assessed with the 10-item version Connor-Davidson Resilience Scale (CD-RISC) (Campbell-Sills and Stein, 2007). Its items are rated on a five-point scale (0 = *not at all true* to 4 = *true nearly all the time*), and total score range from 0 to 40, with higher scores corresponding to higher levels of resilience. The Oslo Social Support Scale (OSSS-3) (Kocalevent et al., 2018) was used to assess social support, and it is composed of 3 items, with a total score ranging from 3 to 14, where higher values represent higher levels of social support.

2.3. Statistical analyses

All analyses were conducted with RStudio, R version 4.1.2 (R Core Team, 2021).

2.3.1. Missing data

We inspected missing data using the "skimr" R package (Michael Quinn, 2019), and included only those variables with at least 90 % of observed data in the model. Missing data were imputed by using the R package "missRanger" (Wright and Ziegler, 2017), which is based on the algorithm of "missForest" (Daniel J. Stekhoven, 2022) and uses a random forest approach. The parameter "num.trees" was set at 5000, and the out-of-bag errors were calculated for each variable to measure accuracy (meaning how many labels the model got right out of the total number of predictions) ranging from 0 (better performance) to 1 (worse performance).

2.3.2. Descriptive statistics of the sample and univariate analyses

Socio-demographic and clinical characteristics of the sample were provided. Two-sample *t*-test and chi-squares tests were used to study the differences in these variables between individuals with and without pre-pandemic lifetime mental disorders, and between those individuals that required hospitalization due to COVID-19 versus those who did not. Significance was set at $p < 0.05$ after adjusting *p*-values for multiple comparisons using Bonferroni correction.

2.3.3. Network analysis

Network analysis was performed to explore the relationships between mental disorders symptoms (i.e., depression, anxiety, STB, and traumatic stress), resilience, and social support in persons diagnosed with COVID-19 during the first wave of the pandemic. In addition, network results for patients reporting pre-pandemic lifetime mental disorders (i.e., depression, anxiety disorder, substance use disorder, bipolar disorder, or any other mental disorder) were compared to those without a history of mental disorder before the pandemic, and results from hospitalized patients were compared to non-hospitalized ones. Given the high heterogeneity of depressive symptoms (Goldberg, 2011), broadening from cognitive, to motor or sleep alterations, we choose to introduce PHQ-8 individual items independently in the networks. All the other scales' scores were introduced as the total score to avoid Berkson's bias (i.e., selecting a clinical population by symptom sum-scores negatively impacts the recovery performance of networks) (de Ron et al., 2021).

Network structures were estimated using Gaussian Markov random field (Costantini et al., 2015; Lauritzen, 1996) with the EBICglasso model. A nonparanormal transformation of the data was applied before the network estimation as data did not follow a normal distribution (Epskamp et al., 2018a). To control for spurious connections in the network estimation, an optimal regularization parameter was selected by using graphical LASSO (Tibshirani, 1996) and extended Bayesian information criterion (EBIC) (Chen et al., 2008). A threshold was also used to remove edges not surviving *p*-value <0.05.

In the network, nodes represent the studied variables and edges the bidirectional and undirected correlation between each pair of nodes. Thicker and more saturated edges represented stronger correlations; blue and red edges indicated positive and negative partial correlations, respectively.

Network centrality measures (Bringmann et al., 2019) of expected influence, betweenness, and closeness of different nodes were explored (Epskamp et al., 2018b). Expected influence is defined as the sum of all edges extending from a given node, maintaining the sign of each edge (Robinaugh et al., 2016). Betweenness is the number of times the node lies within the shortest path between two other nodes (Brandes, 2010). Closeness is the inverse of the average shortest path length between a node and other nodes, and measures how close the symptom is linked to other symptoms (Rubinov and Sporns, 2010). The connectivity, which provides general information on the dynamics of the network and the connections between specific communities in the network, was explored with one- and two-steps bridge expected influence, defined as the sum of the value of all edges between a node and all nodes that are not in the same community.

The accuracy of edge weights was measured by the 95 % confidence intervals (CIs) computed through bootstrapping (Efron, 1979). The centrality indices' stability was quantified using a case-dropping bootstrap procedure, and the correlation stability coefficient (CS-coefficient) between centrality indices for the full sample was calculated. CS-coefficient represents the maximum proportion of cases that can be dropped, such that with 95 % probability the correlation between the original centrality indices and centrality of networks based on subsets is 0.7.

To examine whether network structure changes among patients with and without a history of mental disorders and among hospitalized and not hospitalized patients, we separately assessed differences in network structure, global strength, and significant edges in both groups. Statistical significance was evaluated by a p-value <0.05.

Network estimation and accuracy were conducted by the "bootnet" R package (Epskamp et al., 2018b) and "qgraph" R package (Epskamp et al., 2012). Network comparison was conducted by "Network Comparison Test" R package (van Borkulo et al., 2022).

3. Results

3.1. Characteristics of the sample

A total of 2084 COVID-19 patients were included in the analysis. The socio-demographic and clinical characteristics of the whole sample are available in Table 1. 22.9 % (n = 500) of the sample have symptoms compatible with current depression according to the PHQ-8 score in the context of COVID-19 infection, and 30 % (n = 471) with GAD according to the GAD-7 score. According to the PCL-5 score, 408 individuals (19.5 %) have symptoms compatible with PTSD. A psychiatric comorbidity was present in 16 % of the individuals (n = 347), with the most common comorbidity being anxiety and depression (n = 76; 22 %).Subjects with pre-existing mental disorders were significantly younger and were more likely to be female. Individuals with pre-existing mental disorders presented significantly higher rates of depressive, anxiety, and post-traumatic symptoms, but had less social support and were less resilient. There were no differences between groups in terms of hospitalization/ICU rates, or the presence of medical comorbidities (see Table 1 for further details). Socio-demographic and clinical differences according to hospitalization due to COVID-19 infection in the whole sample are available in Table S1 in the Supplement.

3.2. Missing data

Among the variables presenting missing data, ten of them presented <10 % of missing values. Of these, eight presented <1 % of missing values. Errors estimated during the imputation of missing data were <5 %.

3.3. Network structure of the total sample

The network estimated using all cases (n = 2084) and including 13 variables is presented in Fig. 1. The edges with the greatest weight in the network were those connecting "social support" and "resilience" (0.94), "depression" and "anhedonia" (0.47), and "anxiety" and "trauma" (0.40), as displayed in Fig. 1 and detailed in the weight matrix (Supplement, Table S2). Information relative to the centrality measures is depicted in Fig. 2. Specifically, "anxiety" and "depression" presented consistently high centrality measures, with "anxiety" reaching the highest values. "Social support" and "resilience" showed high expected influence and the lowest closeness in the whole network, differing in values of betweenness. "Anhedonia" and "trauma" presented an average expected influence, low betweenness, and high closeness. Among the other variables, "guilt" displayed the highest value of betweenness, while "suicidality" presented the lowest scores in centrality measures. "Anxiety" was the variable that better connected the different communities of the network as denoted by the one- and two-steps bridge expected influence (Supplement, Fig. S1). Bootstrapping indicated good accuracy and stability with narrow confidence intervals for edge weights and stable centrality estimates for expected influence and bridge expected influence (CS (cor = 0.7) = 0.75) (Supplement, Figs. S2, S3, S4).

Table 1
Socio-demographic and clinical characteristics of the global sample and according to previous psychiatric history.

	Global	Psychiatric	Non-psychiatric	Test, p-value
	N = 2084	n = 848	n = 1236	
Sex (N, % females)	1141, 55.5	552, 65.6	589, 48.0	$\chi^2 = 63.0$; $p < 0.001$**
Age (mean, SD)	56.2 (17.9)	53.9 (17.5)	57.7 (18.0)	$t = 4.8$; $p < 0.001$**
Hospitalization (N, %)	1107, 56.2	426, 52.9	681, 58.5	$\chi^2 = 6.2$; $p = 0.169$
ICU (N, %)	118, 6.2	44, 5.6	74, 6.5	$\chi^2 = 0.6$; $p = 0.999$
Medical comorbidities (N, %)	924, 44.3	388, 45.8	536, 43.4	$\chi^2 = 1.2$; p = 0.999
Financial problems for COVID-19 (N, %)	598, 29.3	264, 31.8	334, 27.6	$\chi^2 = 4.3$; $p = 0.494$
Active workers (N, %)	991, 47.8	407, 48.3	584, 47.5	$\chi^2 = 0.1$; p = 0.999
OSSS-3 score (mean, SD)	10.39 (2.85)	10.56 (2.76)	10.13 (2.95)	$t = -3.44$; p < 0.001**
CD-RISC score (mean, SD)	38.5 (8.2)	36.7 (8.2)	39.7 (7.9)	$t = 8.3$; $p < 0.001$**
Psychiatric history (N, %)	848, 40.7	848, 100.0	NA	NA
AUD	34, 1.7	34, 4.0	NA	NA
Anxiety	681, 33.1	681, 80.3	NA	NA
Bipolar disorder	37, 1.8	37, 4.4	NA	NA
Depression	401, 19.5	401, 47.3	NA	NA
Suicidal ideation (N, %)	55, 2.7	43, 5.1	12, 1.0	$\chi^2 = 32.6$; p < 0.001**
PHQ-8 score (mean, SD)	14.0 (5.6)	16.3 (5.9)	12.5 (4.7)	$t = -15.9$; p < 0.001**
GAD-7 score (mean, SD)	12.2 (5.3)	14.4 (5.7)	10.8 (4.4)	$t = -15.6$; p < 0.001**
PCL-5 score (mean, SD)	3.1 (3.5)	4.3 (3.9)	2.3 (2.9)	$t = -12.7$; p < 0.001**

SD = standard deviation; ICU = intensive care unit; NA = not applicable; OSSS-3 = Oslo Social Support Scale; CD-RISC = The Connor-Davidson Resilience Scale; AUD = alcohol use disorder; PHQ-9 = Patient Health Questionnaire-9 scale; GAD-7 = General Anxiety Disorder-7 scale; PCL-5 = Posttraumatic Stress Disorder Checklist for DSM-5. Medical comorbidities included at least one positive answer at the Self-Administred Medical Comorbidity Questionnaire (SCQ); Suicidal ideation is considered as a positive result at the Columbia-Suicide Severity Rating Scale (C-SSRS) in the last 30 days. All p are adjusted for multiple comparisons using Bonferroni correction.
** Significant at $p < 0.001$.

3.4. Network comparisons

Networks comparing patients with and without psychiatric diagnoses did not differ in both network structure (p = 0.63) or global strength (p = 0.61) (Supplement, Fig. S5). Looking at the individual edges, edges connecting "motor" and "anxiety" (p = 0.04), and "motor" and "trauma" (p = 0.01) were greater in people with psychiatric diagnoses, while edge connecting "energy" and "motor" (p = 0.04) was smaller in people without psychiatric diagnoses.

Networks comparing patients who were hospitalized or not hospitalized did not differ in both network structure (p = 0.22) or global strength (p = 0.73) (Supplement, Fig. S6). Looking at the individual edges, the edge connecting "depression" and "energy" ($p < 0.01$) was significantly greater in hospitalized people, while edges connecting

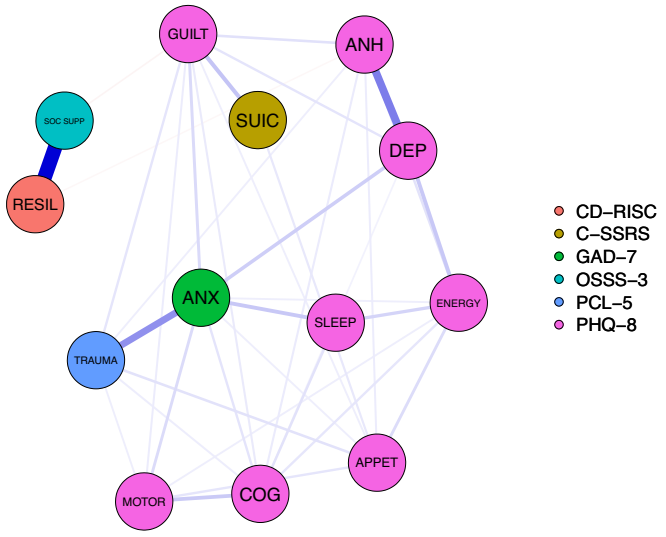

Fig. 1. Graphical representation of the estimated network model. Pink nodes represent depressive symptoms measured with the PHQ-8 scale, the green node represents anxiety symptoms measured with the GAD-7 scale, and the blue node represents the trauma symptoms measured with the PCL-5 scale. The yellow node represents suicidal behavior measured with the C-SSRS. Orange and light blue nodes represent respectively resilience and social support data measured with the CD-RISC and OSSS-3 scales. Blue links indicate positive effects and red links negative effects (SOC SUPP - GUILT and RESIL - ANH). The edge thickness represents the strength of the association between symptom nodes.
Abbreviations: GAD-7 total score, ANX: anxiety; PHQ-8 items: DEP: "sad mood"; ANH: "anhedonia"; ENERGY: "energy"; COG: "concentration"; GUIL: "guilty"; MOTOR: "motor"; APPET: "appetite"; SLEEP: "sleep"; TRAUMA: Trauma; CD-RISC total score, RESIL: "resilience"; OSSS-3 total score, SOC SUPP: "Social Support"; C-SSRS score, SUIC: suicidal behavior. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

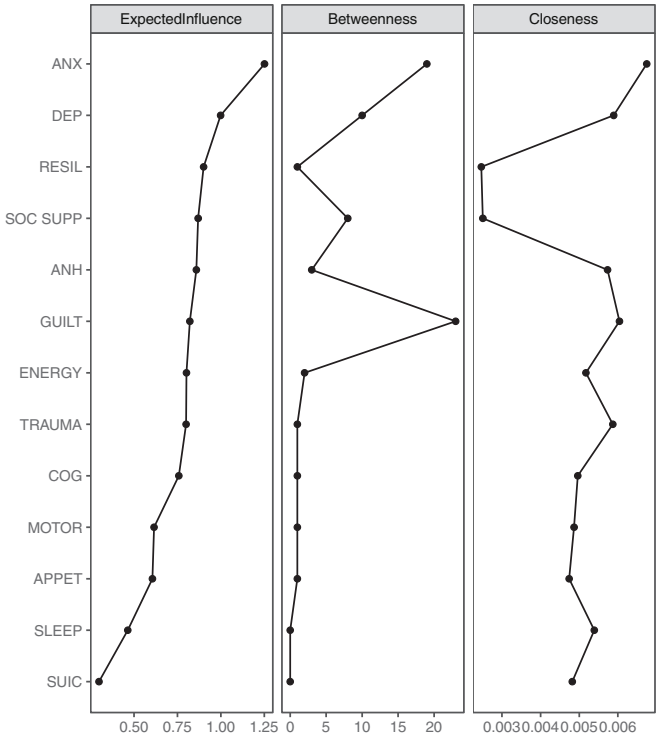

Fig. 2. Centrality Plots for EBICglasso network depicting the expected influence, betweenness and closeness of each node (variable). Abbreviations: GAD-7 total score, ANX: anxiety; PHQ-8 items, DEP: "sad mood"; ANH: "anhedonia"; ENERGY: "energy"; TRAUMA: Trauma; COG: "concentration"; GUIL: "guilty"; MOTOR: "motor"; APPET: "appetite"; SLEEP: "sleep"; CD-RISC total score, RESIL: "resilience"; OSSS-3 total score, SOC SUPP: "Social Support"; C-SSRS score, SUIC: suicidal behavior.

"depression" and "appetite" ($p < 0.01$), and "anxiety" and "trauma" ($p = 0.04$) were smaller.

4. Discussion

The present investigation estimated the network structures of symptoms of anxiety, depression, traumatic stress, suicidal behavior, resilience, and social support in a large sample of patients with COVID-19 during the first wave of the pandemic in Spain, and how these structures vary among patients with severe COVID-19 outcomes (i.e., hospitalization) or with a pre-existing psychiatric disorder. In general, network structures were stable and showed high accuracy. Our results highlighted the central role of anxiety and depression in patients with COVID-19 during the first months of the pandemic, consistent with previous findings (Bai et al., 2022; Cai et al., 2022; Liu et al., 2022). Indeed, during the first wave of COVID-19, both anxiety and depressive symptoms were prevalent both in the general population and in patients with COVID-19 (González-Sanguino et al., 2020). The pandemic and associated lockdown measures led to feelings of uncertainty, fear, and social isolation, which might have contributed to the development of mental health conditions. Anxiety also showed to be a bridge symptom between depressive symptoms and post-traumatic stress symptoms, meaning that it connects these different clusters of symptoms. The reciprocal nature of the relationship between anxiety and PTSD or depression severity is well-known and indicates that these psychopathological dimensions are deeply intertwined (Michopoulos et al., 2017; Norr et al., 2016). Bridge symptoms constitute priority therapeutic targets since the deactivation of these symptoms might prevent the development of other comorbid, simultaneous, symptoms (Cramer and Borsboom, 2015). Thus, clinicians might want to target anxiety as a bridge symptom in order to ameliorate the mental well-being of patients with COVID-19.

Psychological resilience and social support also show a high expected influence and betweenness in our results, but a low closeness, suggesting that although the relationship between the two variables is strong, they are less likely to affect changes in anxiety, depression, or post-traumatic symptoms. Both resilience and social support are important recognized protective factors against psychological distress and help in reducing psychiatric illness burden in the long term (Min et al., 2013; Wang et al., 2018). Reports from longitudinal and cross-sectional studies show that patients with COVID-19 and proper social support or resilience are less likely to manifest anxiety or depression (Li et al., 2021). Also, resilience strategies adopted were heterogeneous among different populations and varied with time, as the global population faced economic losses, fear of unemployment or recession, or other societal issues (Manchia et al., 2022). Our data did not show an influence of resilience or social support on mental health, possibly because the effect of stressful events on psychological outcomes (i.e., anxiety from worrying about economical loss or losing a loved one) and relative coping strategies adopted, became more after several months of the pandemic, while our cross-sectional data were collected during the first COVID-19 wave in Spain, and can give us insight only on the short-term association between COVID-19 and mental health outcomes.

Our result also showed that suicidality was not a central psychopathological dimension in patients with COVID-19 during the first wave of the pandemic, in line with previous reports on the topic (Pérez et al., 2022). Suicidal ideation might be related to several psychopathological dimensions, including depression, but might be considered also a clinical entity on its own (Oquendo and Baca-Garcia, 2014). High-vulnerable groups, such as patients with a pre-existing mental disorder (Gómez-Ramiro et al., 2021), adolescents (Gomez Ramiro et al., 2022),

and COVID-19 survivors might deserve special attention in the long term to reduce undesirable mental health outcomes, including suicide risk. However, given the cross-sectional nature of our data, we can only make conjectures about the impact of COVID-19 on mental health outcomes in the short term. To gain insight into its long-term effects, further longitudinal studies are necessary.

Although we found higher levels of anxiety, depressive and post-traumatic symptoms at the univariate analysis in patients with a previous psychiatric history compared with those without, we were not able to find significant differences in the general network structures between these two populations. However, "motor" and "anxiety" and "motor" and "trauma" edge weights were greater in patients with a previous psychiatric diagnosis, possibly indicating that this subpopulation might present motor-related symptoms (i.e., restlessness) related to more severe anxiety. Patients with previous psychiatric disorders are a fragile population at higher risk of presenting detrimental long-term effects on mental health for COVID-19 compared with the general population and should require specialized treatment and attention (Belz et al., 2022; Vieta et al., 2020b).

Patients hospitalized for COVID-19 did not show significant differences in the network structure compared to non-hospitalized ones. However, hospitalized patients presented more loss of energy as a symptom core of depression compared to non-hospitalized ones. The lack of differences in network estimations might be due to the fact that COVID-19 survivors appear to show an increased risk of developing PTSD, anxiety, and depression in the long, rather than in the short (Kyzar et al., 2021). However, recent evidence shows that psychiatric symptoms and poor sleep quality tend to slowly recover after COVID-19 infection in previously hospitalized COVID-19 survivors (Fernández-De-Las-Peñas et al., 2022). This result could also mean that both subpopulations of patients could have similar responses to the same interventions (Fried and Robinaugh, 2020), pointing to the need for a precision public health approach to psychopathology in the context of an acute pandemic such as COVID-19 during the first wave and beyond (Gonda et al., 2022; Stein and Wessely, 2022).

Our study comes with several limitations. First, both our study's cross-sectional design and network analysis cannot reveal causal dynamics between considered variables. Also, participation was voluntary, so we should consider a possible self-selection bias in individuals responding to the survey. Also, although some of the instruments used to evaluate psychopathological symptoms in the population are validated and used widely in research (i.e. PHQ-8) might overestimate the prevalence of certain disorders (Fischer et al., 2023). Moreover, Berkson's bias could apply to our results and could have affected the edges' weights and thus also the centrality measures. The presence of pre-existence mental disorders was self-reported, and it might be possible severe patients with acute symptoms or poor insight, did not enter the study. Finally, when interpreting the data from this cross-sectional study, we should pay attention to the time and the place at which they were obtained, since we are aware that restriction measures, and the number of COVID-19 cases or deaths, were extremely heterogeneous over time and in different places worldwide, thus preventing generalizability of our results. However, our study gives an insight into the psychopathological features of patients with COVID-19 in Spain, which suffered several pandemic waves, and being one of the most affected European nations (Pacchiarotti et al., 2020). Also, this cross-sectional study includes a large number of patients and a prospective-follow up of this cohort is currently underway, so longitudinal data would be further analyzed in the near future. A study demonstrating that anxiety and depression are central symptoms in patients with COVID-19 using network analysis is an innovative approach that can provide valuable insights into the complex interactions between psychiatric symptoms and COVID-19 infection. Network analysis allows for the investigation of the relationships between symptoms as a whole system, rather than simply analyzing individual symptoms in isolation, thus offering a more comprehensive understanding of the psychological impact of the pandemic.

5. Conclusions

COVID-19 pandemic increased the burden of mental illness in the worldwide population. Patients with COVID-19 infection might experience anxiety, depression, or PTSD. Anxiety might be a key treatment target in the general population since its treatment might prevent other mental health adverse outcomes. While our analysis did not reveal statistically significant differences between patients with pre-existing mental disorders and those without, it is important to consider the potential long-term effects on psychological outcomes in this population. Further studies are needed to explore this association in more depth and assess the impact of COVID-19 on mental health outcomes over an extended period of time. These findings would provide valuable insights for developing personalized mental health interventions tailored to the needs of highly vulnerable populations.

Declaration of competing interest

GA has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck, Lundbeck/Otsuka, and Angelini, with no financial or other relationship relevant to the subject of this article. AF has received CME-related educational support from Lundbeck, not related to the subject of this article. AM has received grants and served as consultant, advisor or CME speaker for the following entities: Angelini, Idorsia, Lundbeck, Pfizer, Takeda, outside of the submitted work. EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, AbbVie, Adamed, Angelini, Biogen, Boehringer-Ingelheim, Celon Pharma, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Janssen, Lundbeck, Merck, Novartis, Orion Corporation, Organon, Otsuka, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris, outside the submitted work.

Acknowledgments

G.F. received the support of a fellowship from "la Caixa" Foundation (ID 100010434); her fellowship code is LCF/BQ/DR21/11880019. AGP receives support from an educational grant from Spanish Ministry of Health, Instituto de Salud Carlos III (CM21/00094) and by the European Social Fund Plus (FSE+). Gerard Anmella is supported by a Rio Hortega 2021 grant (CM21/00017) from the Spanish Ministry of Health financed by the Instituto de Salud Carlos III (ISCIII) and co-financed by the Fondo Social Europeo Plus (FSE+). AM thanks the support of the Spanish Ministry of Science and Innovation (PI19/00672) integrated into the Plan Nacional de I + D + I and co-financed by the ISCIII-Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER). EV thanks the support by CIBER - Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM - (CB07/09/0004), the Ministerio de Ciencia e Innovación (PI18/00805, PI21/00787), Instituto de Salud Carlos III – Fondo Europeo de Desarrollo Regional. Unión Europea. "Una manera de hacer Europa", cofinanciado por la Unión Europea; the CERCA Program/Generalitat de Catalunya and Secretaria d'Universitats i Recerca del Departament d'Economia I Coneixement (2021-SGR-01358, 2017SGR881). Departament de Salut, Generalitat de Catalunya, Pla Estratègic de Recerca i Innovació en Salut (PERIS) 2016-2020 (SLT006/17/00357). Thanks to the support of the European Union Horizon 2020 research and innovation program (EU.3.1.1. Understanding health, wellbeing and disease: Grant No 754907 and EU.3.1.3. Treating and managing disease: Grant No 945151). JA thanks the support by Instituto de Salud Carlos III (Ministerio de Ciencia e Innovación) (ISCIII FEDER COV20/00711) and the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017 SGR 452). MP received support from ISCIII-FSE, Spain: Sara Borrell and Miguel Servet grants (grant number CD18/00049 and CP21/00078). HGM

received support from a Margarita Salas postdoctoral grant from the Ministerio de Universidades (España) linked to Universitat de Barcelona and Universitat Pompeu Fabra.

Financial support

This study was supported by the Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación/FEDER: Unión Europea. "Una manera de hacer Europa", cofinanciado por la Unión Europea (grant number PI21/00787) (grant number COV20/00711), (PM, grant number ISCIII, CD18/00049), (grant number ISCIII, FI18/00012), (VPS, grant number PI19/00236); Ayudas para la Formación de Profesorado Universitario, Ministerio de Ciencia, Innovación y Universidades (grant number FPU15/05728); Generalitat de Catalunya (grant number 2021-SGR-01358, 2017SGR452). The funding institutions had no role in the design, analysis, interpretation or submission of publication of the data. No payment was made for writing this article by a pharmaceutical company or other agency. Corresponding authors had full access to all the data in the study and the final responsibility for the decision of submitting for publication.

Ethical standards

The authors assert that all procedures contributing to this study comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

CRediT authorship contribution statement

GF, VO and MDP designed the study and wrote the protocol. Authors GF, VO, MDP, LF, AF, AGP undertook the statistical analysis, and author GF wrote the first draft of the manuscript. All other authors contributed to and have approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.06.034.

References

Bai, W., Zhao, Y.-J., Cai, H., Sha, S., Zhang, Q., Lei, S.-M., Lok, G.K.I., Chow, I.H.I., Cheung, T., Su, Z., Jackson, T., Xiang, Y.-T., 2022. Network analysis of depression, anxiety, insomnia and quality of life among Macau residents during the COVID-19 pandemic. J. Affect. Disord. 311, 181–188. https://doi.org/10.1016/J.JAD.2022.05.061.

Belz, M., Hessmann, P., Vogelgsang, J., Schmidt, U., Ruhleder, M., Signerski-Krieger, J., Radenbach, K., Trost, S., Schott, B.H., Wiltfang, J., Wolff-Menzler, C., Bartels, C., 2022. Evolution of psychosocial burden and psychiatric symptoms in patients with psychiatric disorders during the Covid-19 pandemic. Eur. Arch. Psychiatry Clin. Neurosci. 272, 29–40. https://doi.org/10.1007/S00406-021-01268-6/FIGURES/2.

Borsboom, D., Cramer, A.O.J., 2013. Network Analysis: An Integrative Approach to the Structure of Psychopathology. https://doi.org/10.1146/annurev-clinpsy-050212-185608.

Borsboom, D., Deserno, M.K., Rhemtulla, M., Epskamp, S., Fried, E.I., McNally, R.J., Robinaugh, D.J., Perugini, M., Dalege, J., Costantini, G., Isvoranu, A.M., Wysocki, A. C., van Borkulo, C.D., van Bork, R., Waldorp, L.J., 2021. Network analysis of multivariate data in psychological science. Nat. Rev. Methods Prim. 1, 1–18. https://doi.org/10.1038/s43586-021-00055-w, 2021 1:1.

Bovin, M.J., Marx, B.P., Weathers, F.W., Gallagher, M.W., Rodriguez, P., Schnurr, P.P., Keane, T.M., 2016. Psychometric properties of the PTSD checklist for diagnostic and statistical manual of mental disorders-fifth edition (PCL-5) in veterans. Psychol. Assess. 28, 1379–1391. https://doi.org/10.1037/PAS0000254.

Brandes, U., 2010. A Faster Algorithm for Betweenness Centrality*, 25, pp. 163–177. https://doi.org/10.1080/0022250X.2001.9990249.

Bringmann, L.F., Elmer, T., Epskamp, S., Krause, R.W., Schoch, D., Wichers, M., Wigman, J.T.W., Snippe, E., 2019. What do centrality measures measure in psychological networks? J. Abnorm. Psychol. 128 https://doi.org/10.1037/ABN0000446.

Cai, H., Bai, W., Liu, H., Chen, X., Qi, H., Liu, R., Cheung, T., Su, Z., Lin, J., Tang, Y. lang, Jackson, T., Zhang, Q., Xiang, Y.T., 2022. Network analysis of depressive and anxiety symptoms in adolescents during the later stage of the COVID-19 pandemic. Transl. Psychiatry 12, 1–8. https://doi.org/10.1038/s41398-022-01838-9, 2022 12:1.

Campbell-Sills, L., Stein, M.B., 2007. Psychometric analysis and refinement of the Connor-davidson Resilience Scale (CD-RISC): validation of a 10-item measure of resilience. J. Trauma. Stress. 20, 1019–1028. https://doi.org/10.1002/JTS.20271.

Charpignon, M.L., Ontiveros, J., Sundaresan, S., Puri, A., Chandra, J., Mandl, K.D., Majumder, M.S., 2022. Evaluation of suicides among US adolescents during the COVID-19 pandemic. JAMA Pediatr. 176, 724–726. https://doi.org/10.1001/JAMAPEDIATRICS.2022.0515.

Chen, J., Yuan, X., Sekiguchi, T., 2008. Advanced semiconductor diagnosis by multidimensional electron-beam-induced current technique. Scanning 30, 347–353. https://doi.org/10.1002/SCA.20116.

Costantini, G., Epskamp, S., Borsboom, D., Perugini, M., Mõttus, R., Waldorp, L.J., Cramer, A.O.J., 2015. State of the aRt personality research: a tutorial on network analysis of personality data in R. J. Res. Pers. 54, 13–29. https://doi.org/10.1016/J.JRP.2014.07.003.

Cramer, A.O.J., Borsboom, D., 2015. Problems Attract Problems: A Network Perspective on Mental Disorders.

de Hert, M., Mazereel, V., Stroobants, M., de Picker, L., van Assche, K., Detraux, J., 2022. COVID-19-related mortality risk in people with severe mental illness: a systematic and critical review. Front. Psychiatry 12, 798554. https://doi.org/10.3389/FPSYT.2021.798554/FULL.

de Ron, J., Fried, E.I., Epskamp, S., 2021. Psychological networks in clinical populations: investigating the consequences of Berkson's bias. Psychol. Med. 51, 168–176. https://doi.org/10.1017/S0033291719003209.

Efron, B., 1979. Bootstrap Methods: Another Look at the Jackknife. doi:10.1214/aos/1176344552, 7, pp. 1–26. https://doi.org/10.1214/AOS/1176344552.

Epskamp, S., Cramer, A.O.J., Waldorp, L.J., Schmittmann, V.D., Borsboom, D., 2012. qgraph: network visualizations of relationships in psychometric data. J. Stat. Softw. 48, 1–18. https://doi.org/10.18637/JSS.V048.I04.

Epskamp, S., Borsboom, D., Fried, E.I., 2018a. Estimating psychological networks and their accuracy: a tutorial paper. Behav. Res. Methods 50, 195–212. https://doi.org/10.3758/S13428-017-0862-1/FIGURES/9.

Epskamp, S., Borsboom, D., Fried, E.I., 2018b. Estimating psychological networks and their accuracy: a tutorial paper. Behav. Res. Methods 50, 195–212. https://doi.org/10.3758/s13428-017-0862-1.

Epstein, D., Andrawis, W., Lipsky, A.M., Ziad, H.A., Matan, M., 2020. Anxiety and suicidality in a hospitalized patient with COVID-19 infection. Eur. J. Case Rep. Intern. Med. 7, 1. https://doi.org/10.12890/2020_001651.

Fernández-De-Las-Peñas, C., Martín-Guerrero, J.D., Cancela-Cilleruelo, I., Moro-López-Menchero, P., Rodríguez-Jiménez, J., Pellicer-Valero, O.J., 2022. Trajectory curves of post-COVID anxiety/depressive symptoms and sleep quality in previously hospitalized COVID-19 survivors: the LONG-COVID-EXP-CM multicenter study. Psychol. Med. 1–2. https://doi.org/10.1017/S003329172200006X.

Fico, G., Isayeva, U., de Prisco, M., Oliva, V., Solè, B., Montejo, L., Grande, I., Arbelo, N., Gomez-Ramiro, M., Pintor, L., Carpiniello, B., Manchia, M., Vieta, E., Murru, A., 2022. Psychotropic drug repurposing for COVID-19: a systematic review and meta-analysis. Eur. Neuropsychopharmacol. https://doi.org/10.1016/J.EURONEURO.2022.10.004.

Fischer, F., Zocholl, D., Rauch, G., Levis, B., Benedetti, A., Thombs, B., Rose, M., Kostoulas, P., 2023. Prevalence estimates of major depressive disorder in 27 European countries from the European Health Interview Survey: accounting for imperfect diagnostic accuracy of the PHQ-8. BMJ Ment. Health 26, e300675. https://doi.org/10.1136/bmjment-2023-300675.

Fried, E.I., Robinaugh, D.J., 2020. Systems all the way down: embracing complexity in mental health research. BMC Med. 18, 1–4. https://doi.org/10.1186/S12916-020-01668-W/METRICS.

Goldberg, D., 2011. The heterogeneity of "major depression". World Psychiatry 10, 226. https://doi.org/10.1002/J.2051-5545.2011.TB00061.X.

Gómez-Ramiro, M., Fico, G., Anmella, G., Vázquez, M., Sagué-Vilavella, M., Hidalgo-Mazzei, D., Pacchiarotti, I., Garriga, M., Murru, A., Parellada, E., Vieta, E., 2021. Changing trends in psychiatric emergency service admissions during the COVID-19 outbreak: report from a worldwide epicentre. J. Affect. Disord. 282, 26–32. https://doi.org/10.1016/j.jad.2020.12.057.

Gomez Ramiro, M., Fortea, A., Fortea, L., Fico, G., Gimenez-Palomo, A., Sagué-Vilavella, M., Pons-Cabrera, M.T., Radua, J., Vázquez, M., Baldaquí, N., Colomer, L., Fernández, T.M., Gutierrez, F., Llobet, M., Pujal, E., Lazaro, L., Vieta, E., Baeza, I., 2022. The aftermath of COVID-19 lockdown – mental health among children and adolescent in the psychiatry emergency department.

Gonda, X., Dome, P., Erdelyi-Hamza, B., Krause, S., Elek, L.P., Sharma, S.R., Tarazi, F.I., 2022. Invisible wounds: suturing the gap between the neurobiology, conventional and emerging therapies for posttraumatic stress disorder. Eur. Neuropsychopharmacol. 61, 17–29. https://doi.org/10.1016/J.EURONEURO.2022.05.010.

González-Sanguino, C., Ausín, B., Castellanos, M.Á., Saiz, J., López-Gómez, A., Ugidos, C., Muñoz, M., 2020. Mental health consequences during the initial stage of the 2020 coronavirus pandemic (COVID-19) in Spain. Brain Behav. Immun. 87, 172–176. https://doi.org/10.1016/j.bbi.2020.05.040.

Kessler, R.C., Üstün, B.B., 2004. The World Mental Health (WMH) survey initiative version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). Int. J. Methods Psychiatr. Res. 13, 93–117. https://doi.org/10.1002/MPR.168.

Kocalevent, R.D., Berg, L., Beutel, M.E., Hinz, A., Zenger, M., Härter, M., Nater, U., Brähler, E., 2018. Social support in the general population: standardization of the Oslo social support scale (OSSS-3). BMC Psychol. 6, 1–8. https://doi.org/10.1186/S40359-018-0249-9/TABLES/7.

Kroenke, K., Strine, T.W., Spitzer, R.L., Williams, J.B.W., Berry, J.T., Mokdad, A.H., 2009. The PHQ-8 as a measure of current depression in the general population. J. Affect. Disord. 114, 163–173. https://doi.org/10.1016/J.JAD.2008.06.026.

Kyzar, E.J., Purpura, L.J., Shah, J., Cantos, A., Nordvig, A.S., Yin, M.T., 2021. Anxiety, depression, insomnia, and trauma-related symptoms following COVID-19 infection at long-term follow-up. Brain Behav. Immun. Health 16, 100315. https://doi.org/10.1016/J.BBIH.2021.100315.

Lai, J., Ma, S., Wang, Y., Cai, Z., Hu, J., Wei, N., Wu, J., Du, H., Chen, T., Li, R., Tan, H., Kang, L., Yao, L., Huang, M., Wang, H., Wang, G., Liu, Z., Hu, S., 2020. Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. JAMA Netw. Open 3, e203976. https://doi.org/10.1001/jamanetworkopen.2020.3976.

Lauritzen, S.L., 1996. Graph. Model. 17.

Leonardson, G.R., Kemper, E., Ness, F.K., Koplin, B.A., Daniels, M.C., Leonardson, G.A., 2005. Validity and reliability of the audit and CAGE-AID in Northern Plains American Indians. Psychol. Rep. 97, 161–166. https://doi.org/10.2466/pr0.97.1.161-166.

Li, F., Luo, S., Mu, W., Li, Y., Ye, L., Zheng, X., Xu, B., Ding, Y., Ling, P., Zhou, M., Chen, X., 2021. Effects of sources of social support and resilience on the mental health of different age groups during the COVID-19 pandemic. BMC Psychiatry 21, 1–14. https://doi.org/10.1186/S12888-020-03012-1/FIGURES/2.

Liu, R., Chen, X., Qi, H., Feng, Y., Su, Z., Cheung, T., Jackson, T., Lei, H., Zhang, L., Xiang, Y.T., 2022. Network analysis of depressive and anxiety symptoms in adolescents during and after the COVID-19 outbreak peak. J. Affect. Disord. 301, 463–471. https://doi.org/10.1016/J.JAD.2021.12.137.

Llach, C.D., Anmella, G., 2022. Letter to the editor about the article "Psychiatric disorders in post-acute COVID-syndrome 3 (PDPACS): recommendations for health care professionals" (Falconi A et al., 2022). Eur. Neuropsychopharmacol. 59, 56–57. https://doi.org/10.1016/J.EURONEURO.2022.04.006.

Manchia, M., Gathier, A.W., Yapici-Eser, H., Schmidt, M.v., de Quervain, D., van Amelsvoort, T., Bisson, J.I., Cryan, J.F., Howes, O.D., Pinto, L., van der Wee, N.J., Domschke, K., Branchi, I., Vinkers, C.H., 2022. The impact of the prolonged COVID-19 pandemic on stress resilience and mental health: a critical review across waves. Eur. Neuropsychopharmacol. 55, 22–83. https://doi.org/10.1016/J.EURONEURO.2021.10.864.

Matalon, N., Dorman-Ilan, S., Hasson-Ohayon, I., Hertz-Palmor, N., Shani, S., Basel, D., Gross, R., Chen, W., Abramovich, A., Afek, A., Ziv, A., Kreiss, Y., Pessach, I.M., Gothelf, D., 2021. Trajectories of post-traumatic stress symptoms, anxiety, and depression in hospitalized COVID-19 patients: a one-month follow-up. J. Psychosom. Res. 143, 110399 https://doi.org/10.1016/J.JPSYCHORES.2021.110399.

Mdege, N.D., Lang, J., 2011. Screening instruments for detecting illicit drug use/abuse that could be useful in general hospital wards: a systematic review. Addict. Behav. 36, 1111–1119. https://doi.org/10.1016/j.addbeh.2011.07.007.

Michael Quinn, A.M.E.A. de la R.H.Z. and S.E., 2019. skimr: Compact and Flexible Summaries of Data. R package version 1.0.7. https://CRAN.R-project.org/package=skimr [WWW Document].

Michopoulos, V., Powers, A., Gillespie, C.F., Ressler, K.J., Jovanovic, T., 2017. Inflammation in fear- and anxiety-based disorders: PTSD, GAD, and beyond. Neuropsychopharmacology 42, 254–270. https://doi.org/10.1038/npp.2016.146.

Min, J.A., Yu, J.J., Lee, C.U., Chae, J.H., 2013. Cognitive emotion regulation strategies contributing to resilience in patients with depression and/or anxiety disorders. Compr. Psychiatry 54, 1190–1197. https://doi.org/10.1016/J.COMPPSYCH.2013.05.008.

Miskowiak, K.W., Fugledalen, L., Jespersen, A.E., Sattler, S.M., Podlekareva, D., Rungby, J., Porsberg, C.M., Johnsen, S., 2022. Trajectory of cognitive impairments over 1 year after COVID-19 hospitalisation: pattern, severity, and functional implications. Eur. Neuropsychopharmacol. 59, 82–92. https://doi.org/10.1016/J.EURONEURO.2022.04.004.

Moore, A.A., Seeman, T., Morgenstern, H., Beck, J.C., Reuben, D.B., 2002. Are there differences between older persons who screen positive on the CAGE questionnaire and the Short Michigan alcoholism screening test - geriatric version? J. Am. Geriatr. Soc. 50, 858–862. https://doi.org/10.1046/j.1532-5415.2002.50211.x.

Mortier, P., Vilagut, G., Alayo, I., et al., 2022. Four-month incidence of suicidal thoughts and behaviors among healthcare workers after the first wave of the Spain COVID-19 pandemic. J Psychiatr Res. 149, 10–17. https://doi.org/10.1016/j.jpsychires.2022.02.009.

Nemani, K., Li, C., Olfson, M., Blessing, E.M., Razavian, N., Chen, J., Petkova, E., Goff, D. C., 2021. Association of psychiatric disorders with mortality among patients with COVID-19. JAMA Psychiatry 78, 380–386. https://doi.org/10.1001/JAMAPSYCHIATRY.2020.4442.

Norr, A.M., Albanese, B.J., Boffa, J.W., Short, N.A., Schmidt, N.B., 2016. The relationship between gender and PTSD symptoms: anxiety sensitivity as a mechanism. Pers. Individ. Differ. 90, 210–213. https://doi.org/10.1016/J.PAID.2015.11.014.

Oquendo, M.A., Baca-Garcia, E., 2014. Suicidal behavior disorder as a diagnostic entity in the DSM-5 classification system: advantages outweigh limitations. World Psychiatry 13, 128. https://doi.org/10.1002/WPS.20116.

Pacchiarotti, I., Anmella, G., Fico, G., Verdolini, N., Vieta, E., 2020. A psychiatrist's perspective from a COVID-19 epicentre: a personal account. BJPsych Open 6, e108. https://doi.org/10.1192/bjo.2020.83.

Pérez, V., Elices, M., Vilagut, G., Vieta, E., Blanch, J., Laborda-Serrano, E., Prat, B., Colom, F., Palao, D., Alonso, J., 2022. Suicide-related thoughts and behavior and suicide death trends during the COVID-19 in the general population of Catalonia, Spain. Eur. Neuropsychopharmacol. 56, 4–12. https://doi.org/10.1016/J.EURONEURO.2021.11.006.

Pirkis, J., John, A., Shin, S., DelPozo-Banos, M., Arya, V., Analuisa-Aguilar, P., Appleby, L., Arensman, E., Bantjes, J., Baran, A., Bertolote, J.M., Borges, G., Brečić, P., Caine, E., Castelpietra, G., Chang, S.-S., Colchester, D., Crompton, D., Curkovic, M., Deisenhammer, E.A., Du, C., Dwyer, J., Erlangsen, A., Faust, J.S., Fortune, S., Garrett, A., George, D., Gerstner, R., Gilissen, R., Gould, M., Hawton, K., Kanter, J., Kapur, N., Khan, M., Kirtley, O.J., Knipe, D., Kolves, K., Leske, S., Marahatta, K., Mittendorfer-Rutz, E., Neznanov, N., Niederkrotenthaler, T., Nielsen, E., Nordentoft, M., Oberlerchner, H., O'Connor, R.C., Pearson, M., Phillips, M.R., Platt, S., Plener, P.L., Psota, G., Qin, P., Radeloff, D., Rados, C., Reif, A., Reif-Leonhard, C., Rozanov, V., Schlang, C., Schneider, B., Semenova, N., Sinyor, M., Townsend, E., Ueda, M., Vijayakumar, L., Webb, R.T., Weerasinghe, M., Zalsman, G., Gunnell, D., Spittal, M.J., 2021. Suicide trends in the early months of the COVID-19 pandemic: an interrupted time-series analysis of preliminary data from 21 countries. Lancet Psychiatry 8, 579–588. https://doi.org/10.1016/S2215-0366(21)00091-2.

Posner, K., Brown, G.K., Stanley, B., Brent, D.A., Yershova, K.v., Oquendo, M.A., Currier, G.W., Melvin, G.A., Greenhill, L., Shen, S., Mann, J.J., 2011. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am. J. Psychiatry 168, 1266–1277. https://doi.org/10.1176/APPI.AJP.2011.10111704.

R Core Team, 2021. R: A language and environment for statisticalcomputing. In: R Foundation for Statistical Computing, Vienna, Austria. URL. https://www.R-project.org/.

Robinaugh, D.J., Millner, A.J., McNally, R.J., 2016. Identifying highly influential nodes in the complicated grief network. J. Abnorm. Psychol. 125, 747. https://doi.org/10.1037/ABN0000181.

Rogers, J.P., Chesney, E., Oliver, D., Pollak, T.A., McGuire, P., Fusar-Poli, P., Zandi, M.S., Lewis, G., David, A.S., 2020. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry 7, 611–627. https://doi.org/10.1016/S2215-0366(20)30203-0.

Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. Neuroimage 52, 1059–1069. https://doi.org/10.1016/J.NEUROIMAGE.2009.10.003.

Santomauro, D.F., Mantilla Herrera, A.M., Shadid, J., Zheng, P., Ashbaugh, C., Pigott, D. M., Abbafati, C., Adolph, C., Amlag, J.O., Aravkin, A.Y., Bang-Jensen, B.L., Bertolacci, G.J., Bloom, S.S., Castellano, R., Castro, E., Chakrabarti, S., Chattopadhyay, J., Cogen, R.M., Collins, J.K., Dai, X., Dangel, W.J., Dapper, C., Deen, A., Erickson, M., Ewald, S.B., Flaxman, A.D., Frostad, J.J., Fullman, N., Giles, J.R., Giref, A.Z., Guo, G., He, J., Helak, M., Hulland, E.N., Idrisov, B., Lindstrom, A., Linebarger, E., Lotufo, P.A., Lozano, R., Magistro, B., Malta, D.C., Månsson, J.C., Marinho, F., Mokdad, A.H., Monasta, L., Naik, P., Nomura, S., O'Halloran, J.K., Ostroff, S.M., Pasovic, M., Penberthy, L., Reiner, R.C., Reinke, G., Ribeiro, A.L.P., Sholokhov, A., Sorensen, R.J.D., Varavikova, E., Vo, A.T., Walcott, R., Watson, S., Wiysonge, C.S., Zigler, B., Hay, S.I., Vos, T., Murray, C.J.L., Whiteford, H.A., Ferrari, A.J., 2021. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet 398, 1700–1712. https://doi.org/10.1016/S0140-6736(21)02143-7/ATTACHMENT/927FDFEF-CCD4-4655-AACF-4E7D54DFECF5/MMC1.PDF.

Shevlin, M., Butter, S., McBride, O., Murphy, J., Gibson-Miller, J., Hartman, T.K., Levita, L., Mason, L., Martinez, A.P., McKay, R., Stocks, T.V., Bennett, K.M., Hyland, P., Vallieres, F., Valiente, C., Vazquez, C., Contreras, A., Peinado, V., Trucharte, A., Bertamini, M., Panzeri, A., Bruno, G., Granziol, U., Mignemi, G., Spoto, A., Vidotto, G., Bentall, R.P., 2022. Measurement invariance of the Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder scale (GAD-7) across four European countries during the COVID-19 pandemic. BMC Psychiatry 22, 154. https://doi.org/10.1186/s12888-022-03787-5.

Solé, B., Verdolini, N., Amoretti, S., Montejo, L., Rosa, A.R., Hogg, B., Garcia-Rizo, C., Mezquida, G., Bernardo, M., Martinez-Aran, A., Vieta, E., Torrent, C., 2021. Effects of the COVID-19 pandemic and lockdown in Spain: comparison between community controls and patients with a psychiatric disorder. Preliminary results from the BRIS-MHC STUDY. J. Affect. Disord. 281, 13–23. https://doi.org/10.1016/j.jad.2020.11.099.

Spitzer, R.L., Kroenke, K., Williams, J.B.W., Löwe, B., 2006. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch. Intern. Med. 166, 1092–1097. https://doi.org/10.1001/ARCHINTE.166.10.1092.

Stein, D.J., Wessely, S., 2022. Mental disorders and COVID-19: towards a precision public mental health approach. Eur. Neuropsychopharmacol. 58, 42. https://doi.org/10.1016/J.EURONEURO.2022.02.008.

Stekhoven, Daniel J., 2022. Nonparametric Missing Value Imputation Using Random Forest [WWW Document].

Taquet, M., Luciano, S., Geddes, J.R., Harrison, P.J., 2021. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry 8, 130–140. https://doi.org/10.1016/S2215-0366(20)30462-4/ATTACHMENT/934A6B0C-233B-46D5-8399-8D57682BCB25/MMC1.PDF.

Tibshirani, R., 1996. Regression shrinkage and selection via the Lasso. J. R. Stat. Soc. Ser. B Methodol. 58, 267–288. https://doi.org/10.1111/J.2517-6161.1996.TB02080.X.

Torous, J., Keshavan, M., 2020. COVID-19, mobile health and serious mental illness. Schizophr. Res. 218, 36–37. https://doi.org/10.1016/j.schres.2020.04.013.

Vai, B., Mazza, M.G., Delli Colli, C., Foiselle, M., Allen, B., Benedetti, F., Borsini, A., Casanova Dias, M., Tamouza, R., Leboyer, M., Benros, M.E., Branchi, I., Fusar-Poli, P., de Picker, L.J., 2021. Mental disorders and risk of COVID-19-related mortality, hospitalisation, and intensive care unit admission: a systematic review and meta-analysis. Lancet Psychiatry 8, 797–812. https://doi.org/10.1016/S2215-0366(21)00232-7/ATTACHMENT/8585EDB2-33A6-4543-9454-785618279ED3/MMC4.PDF.

van Borkulo, C.D., van Bork, R., Boschloo, L., Kossakowski, J.J., Tio, P., Schoevers, R.A., Borsboom, D., Waldorp, L.J., 2022. Comparing network structures on three aspects: a permutation test. Psychol. Methods. https://doi.org/10.1037/MET0000476.

Verdolini, N., Amoretti, S., Montejo, L., García-Rizo, C., Hogg, B., Mezquida, G., Rabelo-da-Ponte, F.D., Vallespir, C., Radua, J., Martinez-Aran, A., Pacchiarotti, I., Rosa, A. R., Bernardo, M., Vieta, E., Torrent, C., Solé, B., 2021. Resilience and mental health during the COVID-19 pandemic. J. Affect. Disord. 283, 156–164. https://doi.org/10.1016/J.JAD.2021.01.055.

Vieta, E., Pérez, V., Arango, C., 2020a. Psychiatry in the aftermath of COVID-19. Rev. Psiquiatr. Salud Ment. 13, 105–110. https://doi.org/10.1016/j.rpsm.2020.04.004.

Vieta, E., Pérez, V., Arango, C., 2020b. Psychiatry in the aftermath of COVID-19. Rev. Psiquiatr. Salud Ment. 13, 105. https://doi.org/10.1016/J.RPSMEN.2020.04.004.

Wang, J., Mann, F., Lloyd-Evans, B., Ma, R., Johnson, S., 2018. Associations between loneliness and perceived social support and outcomes of mental health problems: a systematic review. BMC Psychiatry 18, 1–16. https://doi.org/10.1186/S12888-018-1736-5/TABLES/6.

Wright, M.N., Ziegler, A., 2017. ranger: A Fast Implementation of Random Forests for High Dimensional Data in C++ and R. J. Stat. Softw. 77 (1), 1–17. https://doi.org/10.18637/jss.v077.i01.

Wu, Y., Levis, B., Riehm, K.E., Saadat, N., Levis, A.W., Azar, M., Rice, D.B., Boruff, J., Cuijpers, P., Gilbody, S., Ioannidis, J.P.A., Kloda, L.A., McMillan, D., Patten, S.B., Shrier, I., Ziegelstein, R.C., Akena, D.H., Arroll, B., Ayalon, L., Baradaran, H.R., Baron, M., Bombardier, C.H., Butterworth, P., Carter, G., Chagas, M.H., Chan, J.C.N., Cholera, R., Conwell, Y., De Man-Van Ginkel, J.M., Fann, J.R., Fischer, F.H., Fung, D., Gelaye, B., Goodyear-Smith, F., Greeno, C.G., Hall, B.J., Harrison, P.A., Härter, M., Hegerl, U., Hides, L., Hobfoll, S.E., Hudson, M., Hyphantis, T., Inagaki, M., Jetté, N., Khamseh, M.E., Kiely, K.M., Kwan, Y., Lamers, F., Liu, S.I., Lotrakul, M., Loureiro, S.R., Löwe, B., McGuire, A., Mohd-Sidik, S., Munhoz, T.N., Muramatsu, K., Osório, F.L., Patel, V., Pence, B.W., Persoons, P., Picardi, A., Reuter, K., Rooney, A.G., Santos, I.S., Shaaban, J., Sidebottom, A., Simning, A., Stafford, L., Sung, S., Tan, P.L.L., Turner, A., Van Weert, H.C., White, J., Whooley, M. A., Winkley, K., Yamada, M., Benedetti, A., Thombs, B.D., 2020. Equivalency of the diagnostic accuracy of the PHQ-8 and PHQ-9: a systematic review and individual participant data meta-analysis. Psychol. Med. 50, 1368–1380. https://doi.org/10.1017/S0033291719001314.

Zhou, S.J., Wang, L.L., Yang, R., Yang, X.J., Zhang, L.G., Guo, Z.C., Chen, J.C., Wang, J. Q., Chen, J.X., 2020. Sleep problems among Chinese adolescents and young adults during the coronavirus-2019 pandemic. Sleep Med. 74, 39–47. https://doi.org/10.1016/J.SLEEP.2020.06.001.

Zuromski, K.L., Ustun, B., Hwang, I., Keane, T.M., Marx, B.P., Stein, M.B., Ursano, R.J., Kessler, R.C., 2019. Developing an optimal short-form of the PTSD checklist for DSM-5 (PCL-5). Depress. Anxiety 36, 790–800. https://doi.org/10.1002/DA.22942.